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IN THE UNITED STATES DISTRICT COURT
FOR THE DISTRICT OF NEW JERSEY

NAUTILUS NEUROSCIENCES, INC. and APR APPLIED PHARMA RESEARCH SA,	)	
Plaintiffs,	)	Civil Action No. _____
v.	)	
EDICT PHARMACEUTICALS PVT. LTD.,	)	
Defendant.	)	

COMPLAINT

Plaintiffs Nautilus Neurosciences, Inc. ("Nautilus") and APR Applied Pharma Research SA ("APR") (collectively, "Plaintiffs"), by and through their attorneys, for their Complaint against Defendant Edict Pharmaceuticals Pvt. Ltd. ("Defendant"), hereby allege as follows:

PARTIES

1. Nautilus is a Delaware corporation with its principal place of business at 135 Rte 202/206, Bedminster, New Jersey 07921.

2. APR is a corporation organized under the laws of Switzerland with its principal place of business at Via Corti 5, CH-6828, Balerna, Switzerland.

3. On information and belief, Defendant is a corporation organized and existing under the laws of India with its principal place of business at New No. 1/58, Pudupakkam Main Road, Kelambakkam, Chennai – 603 103, Tamil Nadu, India.

4. On information and belief, Defendant has maintained a U.S. office in this judicial district at 9 Revere Road, Monmouth Junction, New Jersey 08852.

5. On information and belief, Defendant authorized a U.S. agent in this district at 508 Elm Avenue, Moorestown, New Jersey 08057 to act on its behalf in corresponding with the United States Food and Drug Administration ("FDA") regarding Defendant's Abbreviated New Drug Application ("ANDA") No. 202964.

6. On information and belief, Defendant develops and manufactures generic pharmaceutical formulations for sale and use throughout the United States, including in this judicial district.

NATURE OF THE ACTION

7. This is a civil action for infringement of U.S. Patent Nos. 6,974,595 (the "'595 patent"), 7,482,377 (the "'377 patent"), and 7,759,394 (the "'394 patent") (collectively, the "patents-in-suit"), which are attached as Exhibits A, B, and C, respectively.

8. This action is based upon the Patent Laws of the United States, 35 U.S.C. § 1 *et seq.*, and arises out of Defendant's filing of ANDA No. 202964 seeking approval to sell diclofenac potassium for oral solution 50 mg prior to the expiration of the patents-in-suit, which are assigned to and/or exclusively licensed by Plaintiffs and listed in the publication entitled "Orange Book: *Approved Drug Products with Therapeutic Equivalents*."

JURISDICTION AND VENUE

9. This action arises under the patent laws of the United States, 35 U.S.C. § 1 *et seq.*

10. This Court has subject matter jurisdiction pursuant to 28 U.S.C. §§ 1331, 1338(a), and 2201(a).

11. Defendant is subject to personal jurisdiction in this District by virtue of, *inter alia*, its manufacture of generic pharmaceutical formulations for sale and use in this District, its conduct of business in this District, the location of one of its offices in this District, the location of its U.S. agent in this District, its purposeful availment of the rights and benefits of New Jersey law, including its previous admissions that it is subject to personal jurisdiction in New Jersey, *see, e.g.*, *Orexo AB v. Edict Pharms. Pvt. Ltd.*, No. 3:10-cv-05548 (D.N.J. Oct. 26, 2010), and its substantial and continuing contacts with the state of New Jersey.

12. Venue is proper in this district pursuant to 28 U.S.C. §§ 1391(b), (c), and (d) and 1400(b).

THE PATENTS-IN-SUIT

13. The ’595 patent, entitled “Pharmaceutical Compositions Based on Diclofenac,” was duly and legally issued by the United States Patent and Trademark Office (“USPTO”) on December 13, 2005.

14. APR owns the entire right, title, and interest in the ’595 patent. Nautilus is the exclusive licensee of the ’595 patent for the United States.

15. The ’377 patent, entitled “Pharmaceutical Compositions and Methods of Treatment Based on Diclofenac,” was duly and legally issued by the USPTO on January 27, 2009.

16. APR owns the entire right, title, and interest in the '377 patent. Nautilus is the exclusive licensee of the '377 patent for the United States.

17. The '394 patent, entitled "Diclofenac Formulations and Methods of Use," was duly and legally issued by the USPTO on July 10, 2010.

18. APR owns the entire right, title, and interest in the '394 patent. Nautilus is the exclusive licensee of the '394 patent for the United States.

19. Nautilus is the holder of New Drug Application ("NDA") No. 22-165 for diclofenac potassium for oral solution 50 mg, sold in the United States under the trademark CAMBIA. The FDA approved NDA No. 22-165 on June 17, 2009.

20. The patents-in-suit are duly listed in the Orange Book: *Approved Drug Products with Therapeutic Equivalents* for NDA No. 22-165. The claims of the patents-in-suit cover, *inter alia*, various methods of using diclofenac.

ACTS GIVING RISE TO THIS ACTION

21. On information and belief, Defendant reviewed each of the patents-in-suit and certain commercial and economic information regarding CAMBIA and decided to file an ANDA seeking approval to market a generic version of CAMBIA.

22. On information and belief, Defendant submitted ANDA No. 202964 to the FDA to seek approval to engage in the commercial manufacture, use, sale, offer for sale, and/or importation into the United States of generic diclofenac potassium for oral solution 50 mg.

23. Plaintiffs received a letter dated June 8, 2011 from Defendant notifying them that Defendant had filed ANDA No. 202964 with the FDA under section 505(j) of the Federal Food, Drug, and Cosmetic Act ("FDCA") seeking approval to market a generic version of CAMBIA prior to the expiry of the patents-in-suit.

24. The stated purpose of Defendant's June 8, 2011 letter was to notify Plaintiffs that ANDA No. 202964 included a certification under 21 U.S.C. § 355(j)(2)(a)(vii)(IV) ("Paragraph IV Certification") that the claims of the patents-in-suit are invalid, unenforceable, and/or will not be infringed by the commercial manufacture, use, sale, offer for sale, and/or importation into the United States of Defendant's ANDA product.

25. On information and belief, Defendant was necessarily aware of each of the patents-in-suit when Defendant filed ANDA No. 202964 with a Paragraph IV Certification.

26. Attached to the June 8, 2011 letter was a "Detailed Statement" setting forth the factual and legal bases for Defendant's opinion that the patents-in-suit are invalid and/or would not be infringed by the commercial manufacture, use, sale, offer for sale, and/or importation into the United States of Defendant's product.

27. Nautilus received the June 8, 2011 letter no earlier than June 13, 2011. APR received the June 8, 2011 letter no earlier than June 13, 2011. Plaintiffs commenced this action within 45 days of the date upon which they received Defendant's June 8, 2011 letter.

FIRST CLAIM FOR RELIEF

(Infringement of the '595 Patent by Defendant)

28. Paragraphs 1 through 27 are incorporated herein as set forth above.

29. Defendant submitted ANDA No. 202964 with a Paragraph IV Certification to the FDA under section 505(j) of the FDCA to obtain approval to engage in the commercial manufacture, use, sale, offer for sale, and/or importation into the United States of diclofenac potassium for oral solution prior to the expiration of the '595 patent. By submitting this ANDA, Defendant has committed an act of infringement under 35 U.S.C. § 271(e)(2).

30. Unless enjoined by this Court, Defendant, upon FDA approval of ANDA No. 202964, will manufacture, use, sell, offer for sale, and/or import into the United States the proposed generic diclofenac potassium product described in ANDA No. 202964, thereby actively inducing others to infringe or contributing to the infringement of the '595 patent under 35 U.S.C. § 271(b) and/or (c).

31. Plaintiffs will be substantially and irreparably harmed if Defendant is not enjoined from infringing the '595 patent.

32. Plaintiffs do not have an adequate remedy at law.

33. An actual and justiciable controversy exists between the parties with respect to the '595 patent.

34. Defendant was aware of the existence of the '595 patent prior to the filing of ANDA No. 202964 but took such action knowing that it would constitute infringement of the '595 patent.

35. Defendant's actions render this an exceptional case under 35 U.S.C. § 285.

SECOND CLAIM FOR RELIEF

(Infringement of the '377 Patent by Defendant)

36. Paragraphs 1 through 35 are incorporated herein as set forth above.

37. Defendant submitted ANDA No. 202964 with a Paragraph IV Certification to the FDA under section 505(j) of the FDCA to obtain approval to engage in the commercial manufacture, use, sale, offer for sale, and/or importation into the United States of diclofenac potassium for oral solution prior to the expiration of the '377 patent. By submitting this ANDA, Defendant has committed an act of infringement under 35 U.S.C. § 271(e)(2).

38. Unless enjoined by this Court, Defendant, upon FDA approval of ANDA No. 202964, will manufacture, use, sell, offer for sale, and/or import into the United States the proposed generic diclofenac potassium product described in ANDA No. 202964, thereby actively inducing others to infringe or contributing to the infringement of the '377 patent under 35 U.S.C. § 271(b) and/or (c).

39. Plaintiffs will be substantially and irreparably harmed if Defendant is not enjoined from infringing the '377 patent.

40. Plaintiffs do not have an adequate remedy at law.

41. An actual justiciable controversy exists between the parties with respect to the '377 patent.

42. Defendant was aware of the existence of the '377 patent prior to the filing of ANDA No. 202964 but took such action knowing that it would constitute infringement of the '377 patent.

43. Defendant's actions render this an exceptional case under 35 U.S.C. § 285.

THIRD CLAIM FOR RELIEF

(Infringement of the '394 patent by Defendant)

44. Paragraphs 1 through 43 are incorporated herein as set forth above.

45. Defendant submitted ANDA No. 202964 with a Paragraph IV Certification to the FDA under section 505(j) of the FDCA to obtain approval to engage in the commercial manufacture, use, sale, offer for sale, and/or importation into the United States of diclofenac potassium for oral solution prior to the expiration of the '394 patent. By submitting this ANDA, Defendant has committed an act of infringement under 35 U.S.C. § 271(e)(2).

46. Unless enjoined by this Court, Defendant, upon FDA approval of ANDA No. 202964, will manufacture, use, sell, offer for sale, and/or import into the United States the proposed generic diclofenac potassium product described in ANDA No. 202964, thereby actively inducing others to infringe or contributing to the infringement of the ’394 patent under 35 U.S.C. § 271(b) and/or (c).

47. Plaintiffs will be substantially and irreparably harmed if Defendant is not enjoined from infringing the ’394 patent.

48. Plaintiffs do not have an adequate remedy at law.

49. An actual justiciable controversy exists between the parties with respect to the ’394 patent.

50. Defendant was aware of the existence of the ’394 patent prior to the filing of ANDA No. 202964 but took such action knowing that it would constitute infringement of the ’394 patent.

51. Defendant’s actions render this an exceptional case under 35 U.S.C. § 285.

PRAYER FOR RELIEF

WHEREFORE, Plaintiffs pray for judgment as follows:

A. An order decreeing that, by submitting ANDA No. 202964 to the FDA, Defendant has infringed the patents-in-suit under 35 U.S.C. § 271(e)(2);

B. A declaration that, through the commercial manufacture, use, sale, offer for sale, and/or importation into the United States of the proposed generic diclofenac potassium product described in ANDA No. 202964, Defendant will actively induce others to infringe or contribute to the infringement of the patents-in-suit under 35 U.S.C. § 271(b) and (c);

C. An order pursuant to 35 U.S.C. § 271(e)(4)(A) decreeing that the effective date of any approval of ANDA No. 202964 be no earlier than the expiration date of the last to expire of the patents-in-suit, including any applicable extensions;

D. A preliminary and permanent injunction restraining and enjoining Defendant, its officers, agents, attorneys, and employees and those acting in privity or concert with them, from engaging in the commercial manufacture, use, sale, and/or offer for sale within the United States and/or importation into the United States of the diclofenac product described in ANDA No. 202964 or any other product not colorably different from the product of ANDA No. 202964 until the expiration of the last to expire of the patents-in-suit, including any applicable extensions;

E. A declaration that this case is exceptional under 35 U.S.C. § 285;

F. An award of attorney fees, costs, and expenses that Plaintiffs incur in prosecuting this action; and

G. Such other and further relief as the Court may deem just and proper.

Dated: July 20, 2011

CONNELL FOLEY LLP
Attorneys for Plaintiffs
Nautilus Neurosciences, Inc. and
APR Applied Pharma Research SA

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LOCAL CIVIL RULE 11.2 CERTIFICATION

I certify that, to the best of my knowledge, the matter in controversy between these parties is not the subject of any other pending or anticipated litigation in any court or arbitration proceeding, nor are there any non-parties known to Plaintiffs that should be joined to this action, with the exception that the patents-in-suit in this matter are the subject of another action pending in this Court: *Nautilus Neurosciences, Inc. et al. v. Wockhardt USA LLC et al.*, Civil Action No. 2:11-1997 (ES) (D.N.J. April 8, 2011).

Dated: July 20, 2011

s/Liza M. Walsh
Liza M. Walsh

LOCAL CIVIL RULE 201.1 CERTIFICATION

I hereby certify that the above-captioned matter is not subject to compulsory arbitration in that declaratory and injunctive relief is sought.

Dated: July 20, 2011

s/Liza M. Walsh
Liza M. Walsh

EXHIBIT A

US006974595B1

(12) **United States Patent**
Reiner et al.

(10) **Patent No.: US 6,974,595 B1**
(45) **Date of Patent: Dec. 13, 2005**

(54) **PHARMACEUTICAL COMPOSITIONS BASED ON DICLOFENAE**

(75) Inventors: **Alberto Reiner**, Como (IT); **Giorgio Reiner**, Como (IT)

(73) Assignee: **ProEthic Pharmaceuticals, Inc.**, Montgomery, AL (US)

(*) Notice: Subject to any disclaimer, the term of this patent is extended or adjusted under 35 U.S.C. 154(b) by 0 days.

(21) Appl. No.: **09/524,747**

(22) Filed: **Mar. 14, 2000**

Related U.S. Application Data

(63) Continuation-in-part of application No. 09/192,493, filed on Nov. 17, 1998, now abandoned, which is a continuation of application No. PCT/EP97/02709, filed on May 15, 1997.

(30) **Foreign Application Priority Data**

May 17, 1996 (IT) MI96A0992

(51) **Int. Cl.**[7] **A61K 33/00**; A61K 45/06
(52) **U.S. Cl.** **424/722**; 424/717; 562/454; 562/456; 562/457; 560/47; 514/553; 514/557; 514/576
(58) **Field of Search** 424/722, 717; 562/454, 456, 457; 560/47; 514/553, 557, 514/576

(56) **References Cited**

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(Continued)

Primary Examiner—James O. Wilson
Assistant Examiner—Howard V. Owens, Jr.
(74) *Attorney, Agent, or Firm*—Clark G. Sullivan; King & Spalding

(57) **ABSTRACT**

New pharmaceutical compositions for oral use containing Diclofenac together with alkali metal bicarbonates in amounts of from 20 to 80 by weight with respect to Diclofenac are described. These compositions are entirely palatable and free from any unpleasant taste or other side effects; in particular, these formulations permit to obtain in human patients higher C_{max} of the active principle and shorter T_{max} together with a lower coefficient of variation.

43 Claims, 10 Drawing Sheets

OTHER PUBLICATIONS

Mendes, G.B.B., et al; "Comparative bioavailability of two suspension formulations of potassium diclofenac in healthy male volunteers"; Int. J. Clin. Pharmacol. Thr., 32:131-135 (1994).

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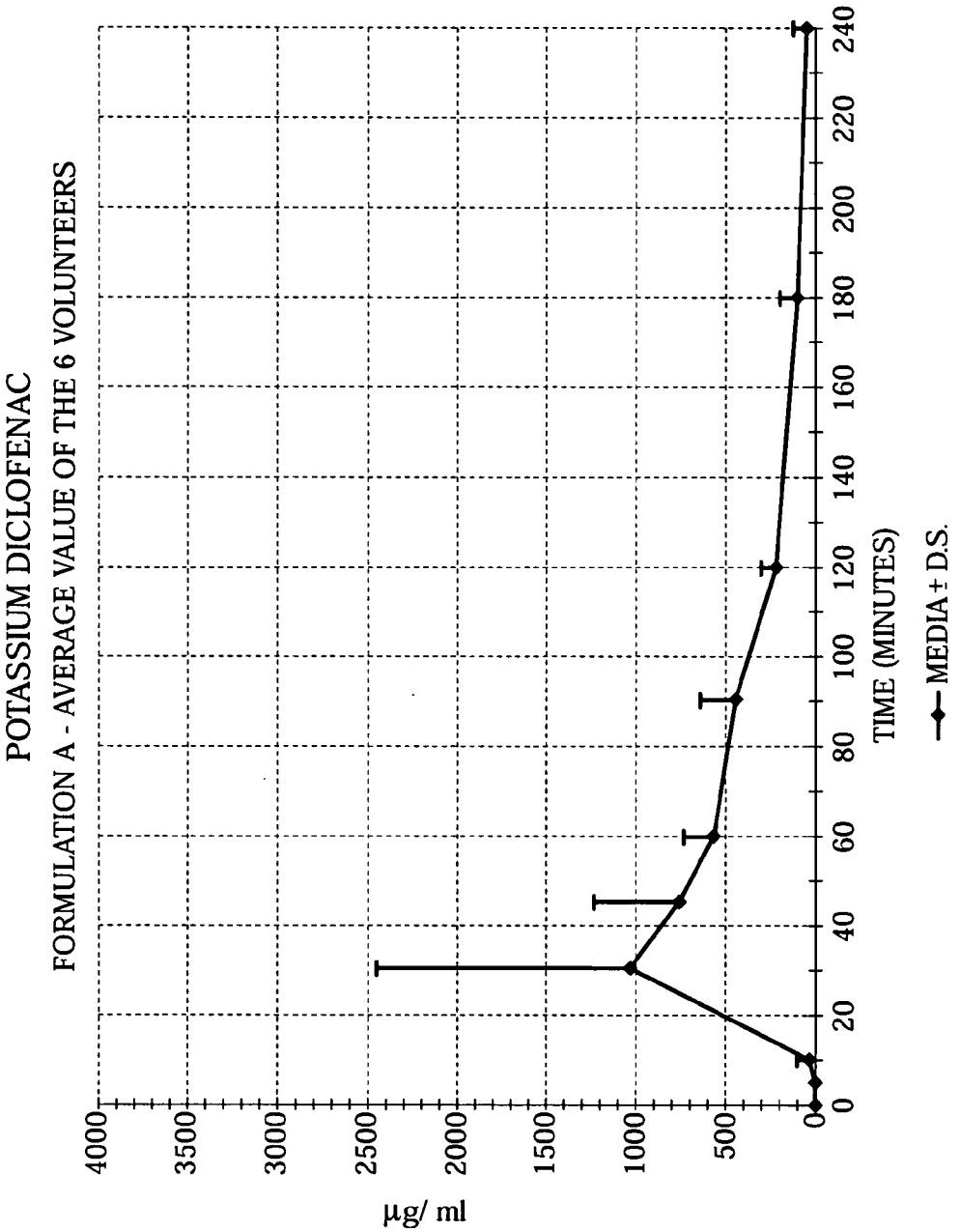

POTASSIUM DICLOFENAC
FORMULATION A - AVERAGE VALUE OF THE 6 VOLUNTEERS
µg/ ml
4000
3500
3000
2500
2000
1500
1000
500
0
0
20
40
60
80
100
120
140
160
180
200
220
240
TIME (MINUTES)
MEDIA ± D.S.

FIG 1

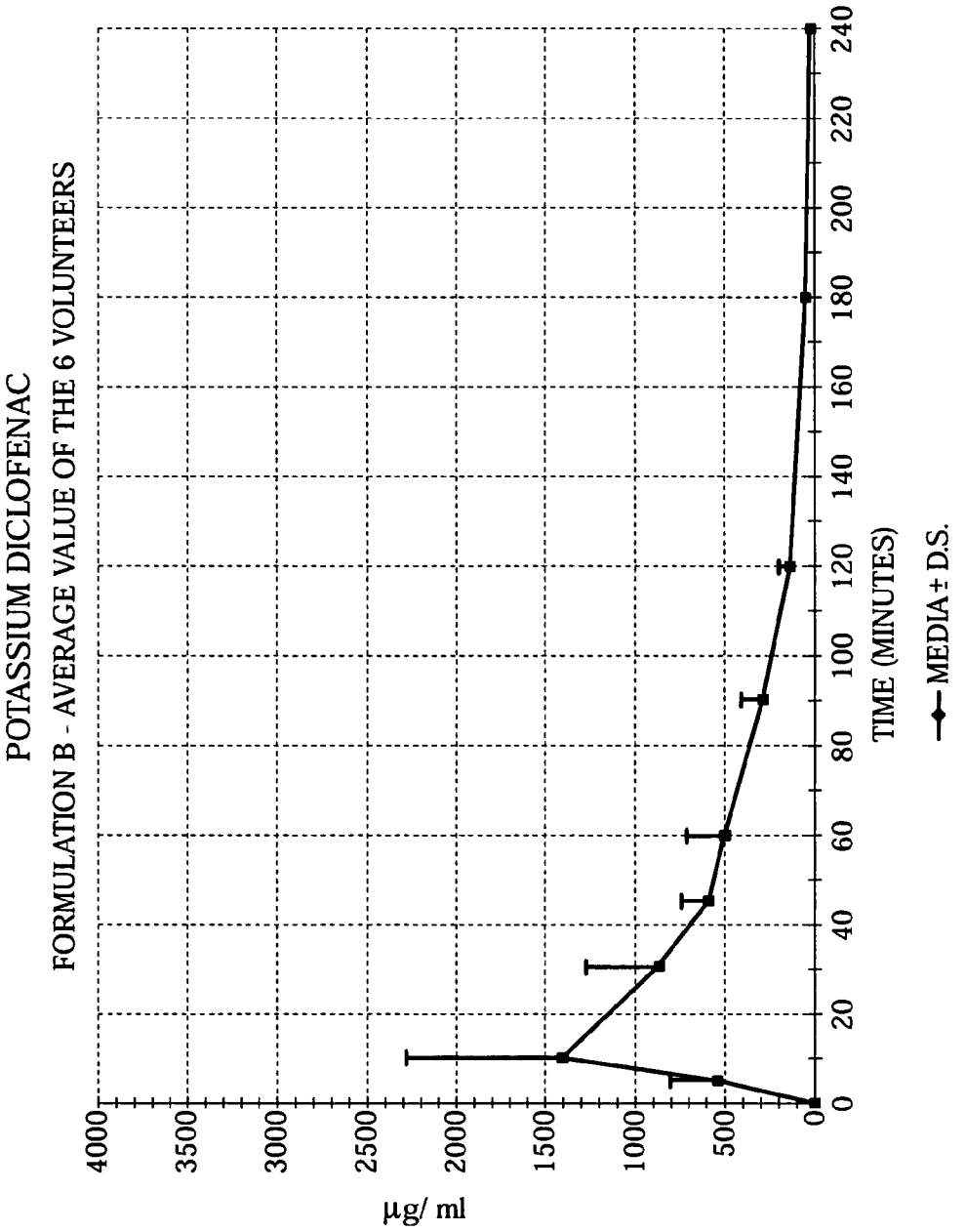

POTASSIUM DICLOFENAC
FORMULATION B - AVERAGE VALUE OF THE 6 VOLUNTEERS
µg/ ml
4000
3500
3000
2500
2000
1500
1000
500
0
0
20
40
60
80
100
120
140
160
180
200
220
240
TIME (MINUTES)
MEDIA ± D.S.

FIG 2

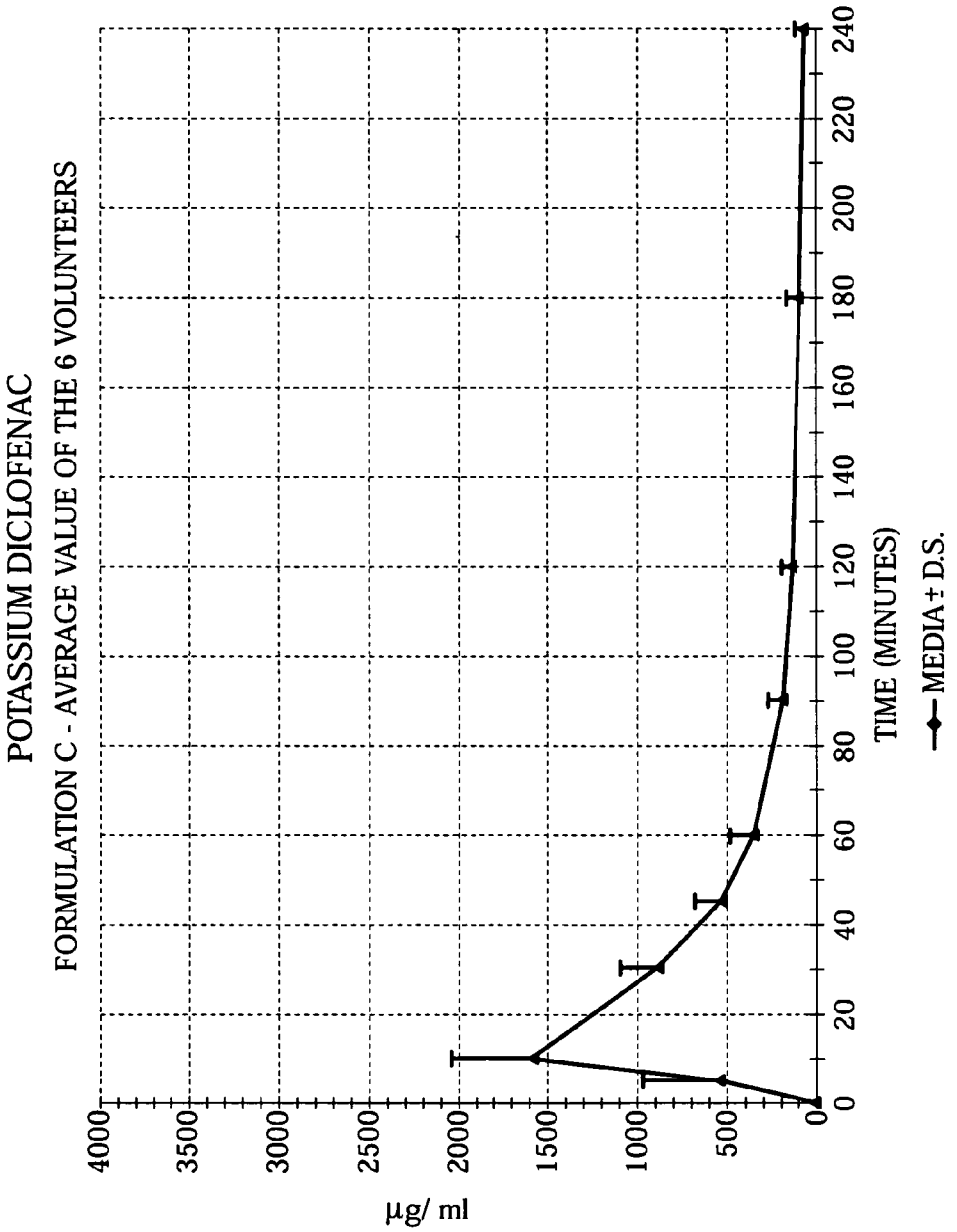

POTASSIUM DICLOFENAC
FORMULATION C - AVERAGE VALUE OF THE 6 VOLUNTEERS
µg/ ml
4000
3500
3000
2500
2000
1500
1000
500
0
0
20
40
60
80
100
120
140
160
180
200
220
240
TIME (MINUTES)
MEDIA ± D.S.

FIG 3

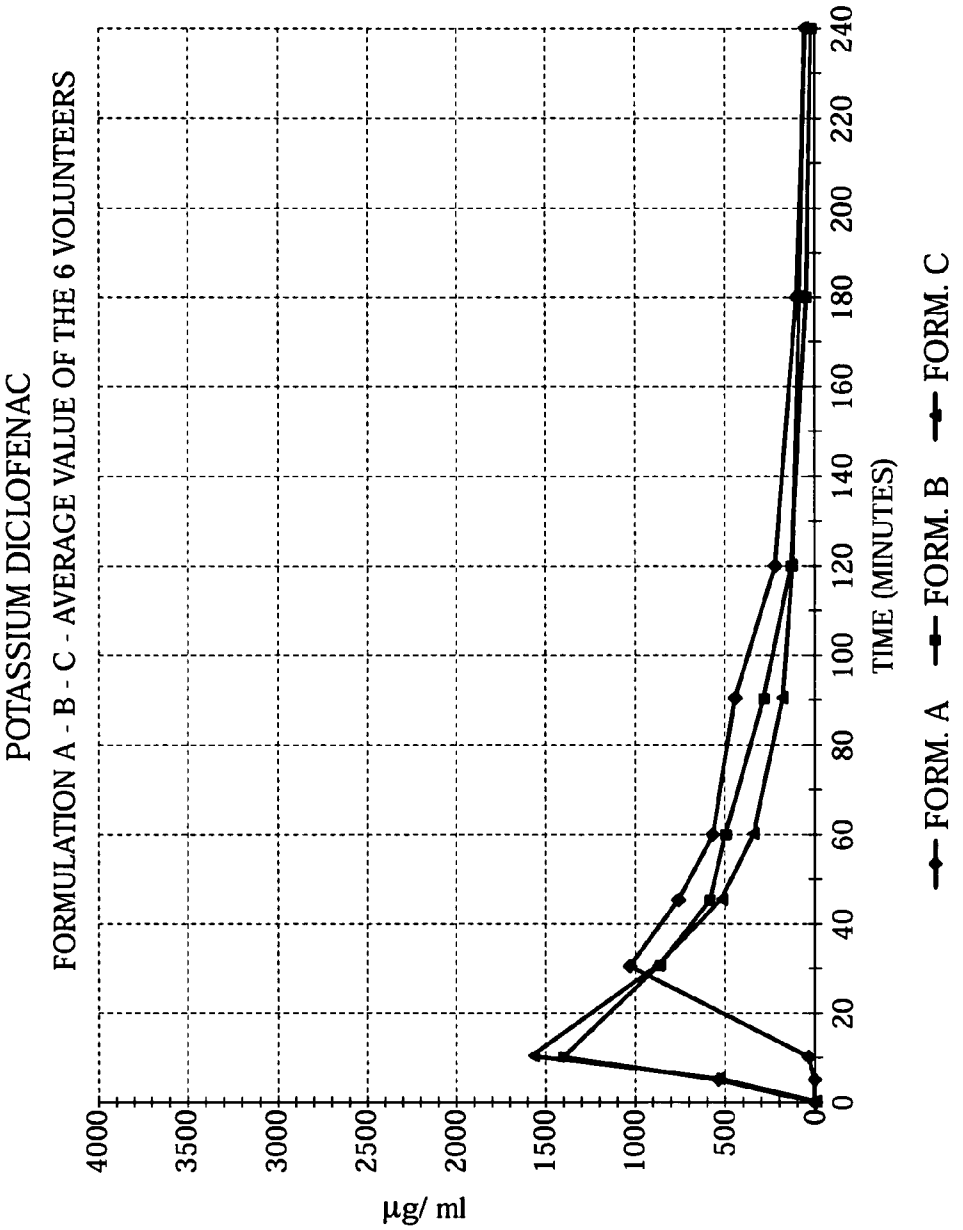

POTASSIUM DICLOFENAC
FORMULATION A - B - C - AVERAGE VALUE OF THE 6 VOLUNTEERS
µg/ ml
4000
3500
3000
2500
2000
1500
1000
500
0
0
20
40
60
80
100
120
140
160
180
200
220
240
TIME (MINUTES)
FORM. A
FORM. B
FORM. C

FIG 4

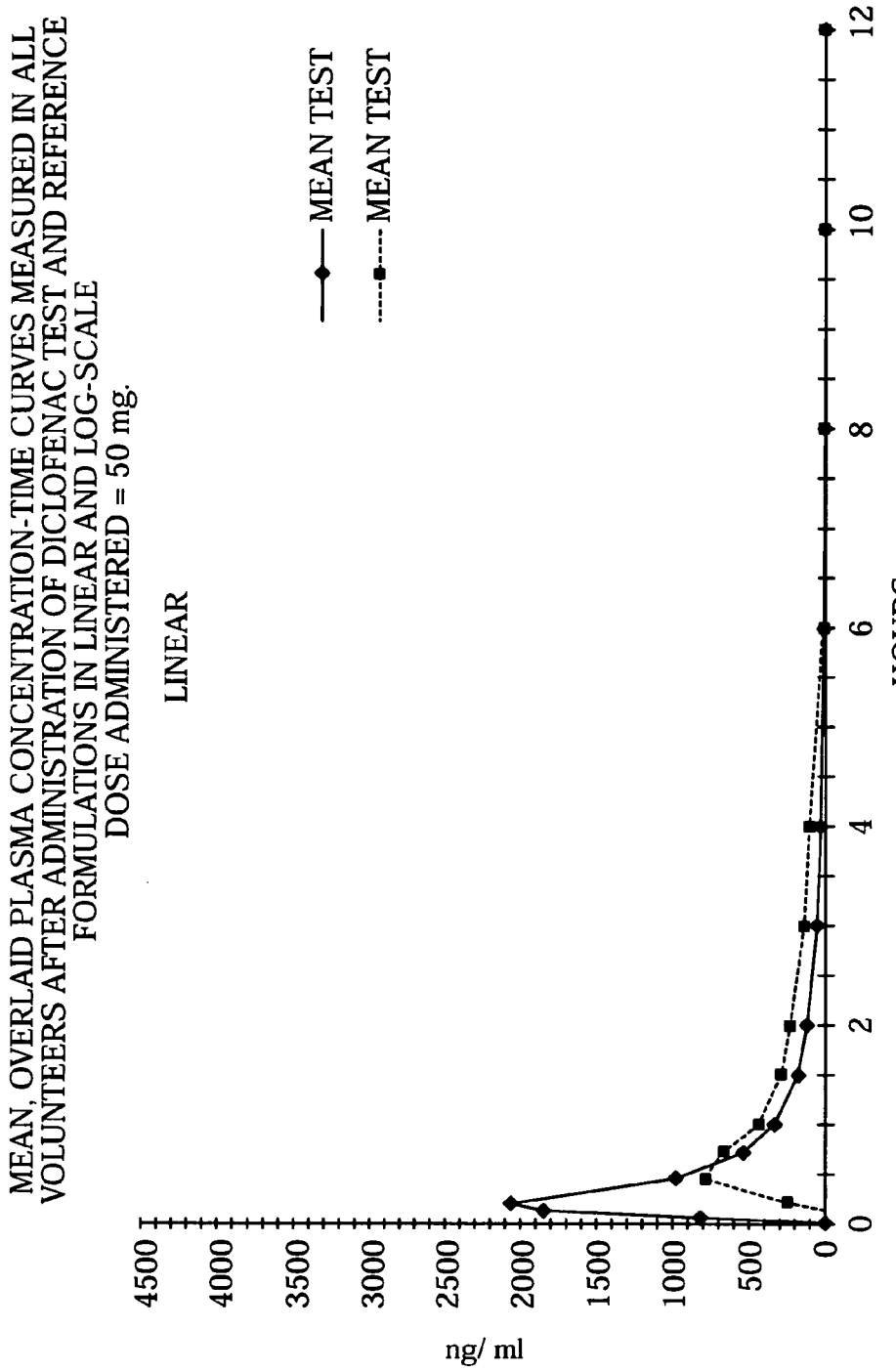

MEAN, OVERLAID PLASMA CONCENTRATION-TIME CURVES MEASURED IN ALL VOLUNTEERS AFTER ADMINISTRATION OF DICLOFENAC TEST AND REFERENCE FORMULATIONS IN LINEAR AND LOG-SCALE
DOSE ADMINISTERED = 50 mg.
LINEAR
MEAN TEST
MEAN TEST
4500
4000
3500
3000
2500
2000
1500
1000
500
0
ng/ ml
0
2
4
6
8
10
12
HOURS

FIG 5

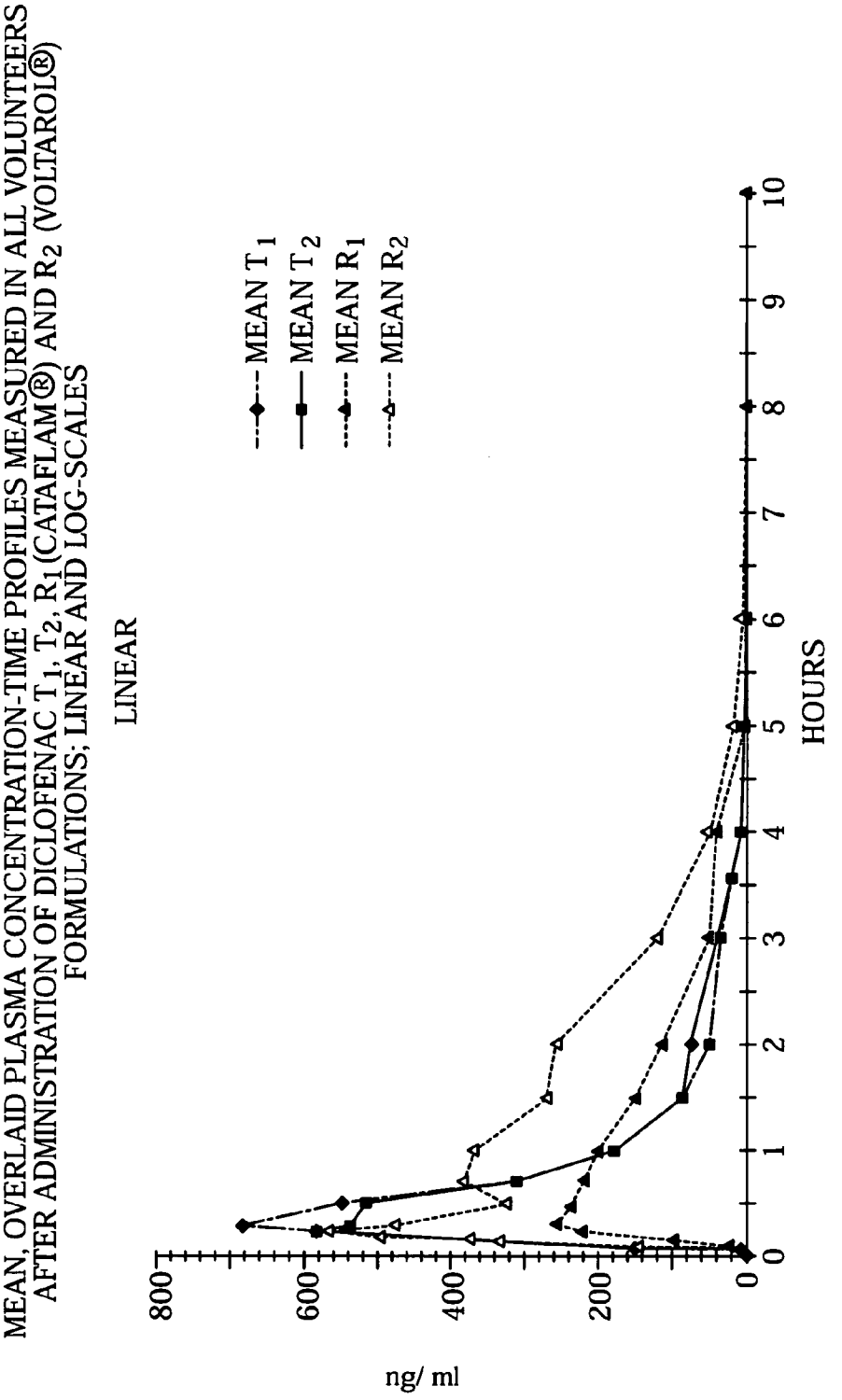

MEAN, OVERLAID PLASMA CONCENTRATION-TIME PROFILES MEASURED IN ALL VOLUNTEERS AFTER ADMINISTRATION OF DICLOFENAC T_1, T_2, R_1(CATAFLAM®) AND R_2 (VOLTAROL®) FORMULATIONS; LINEAR AND LOG-SCALES
LINEAR
MEAN T_1
MEAN T_2
MEAN R_1
MEAN R_2
800
600
400
200
0
ng/ ml
0
1
2
3
4
5
6
7
8
9
10
HOURS

FIG 6

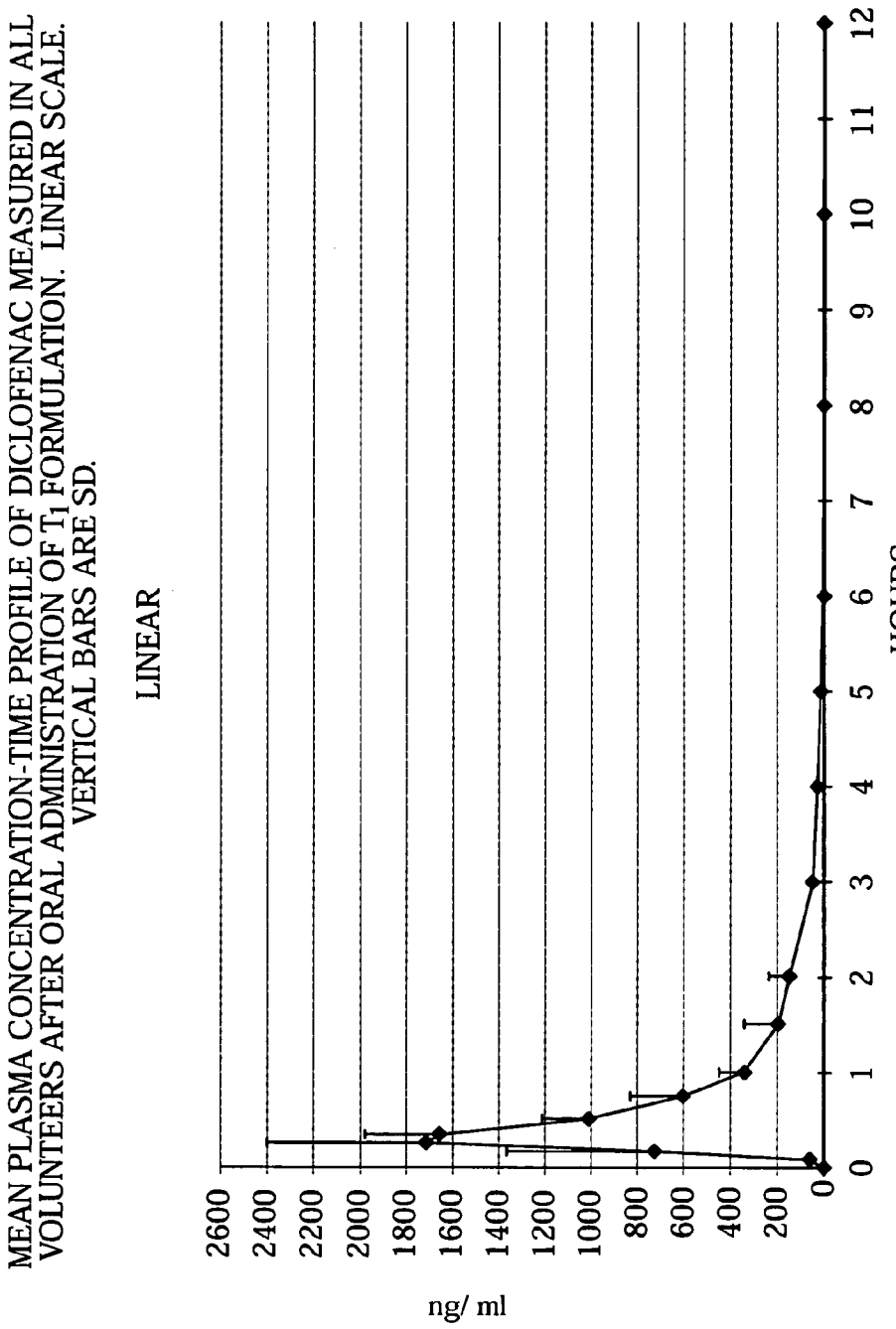

MEAN PLASMA CONCENTRATION-TIME PROFILE OF DICLOFENAC MEASURED IN ALL VOLUNTEERS AFTER ORAL ADMINISTRATION OF T1 FORMULATION. LINEAR SCALE. VERTICAL BARS ARE SD.
LINEAR
ng/ ml
2600
2400
2200
2000
1800
1600
1400
1200
1000
800
600
400
200
0
0
1
2
3
4
5
6
7
8
9
10
11
12
HOURS

FIG 7

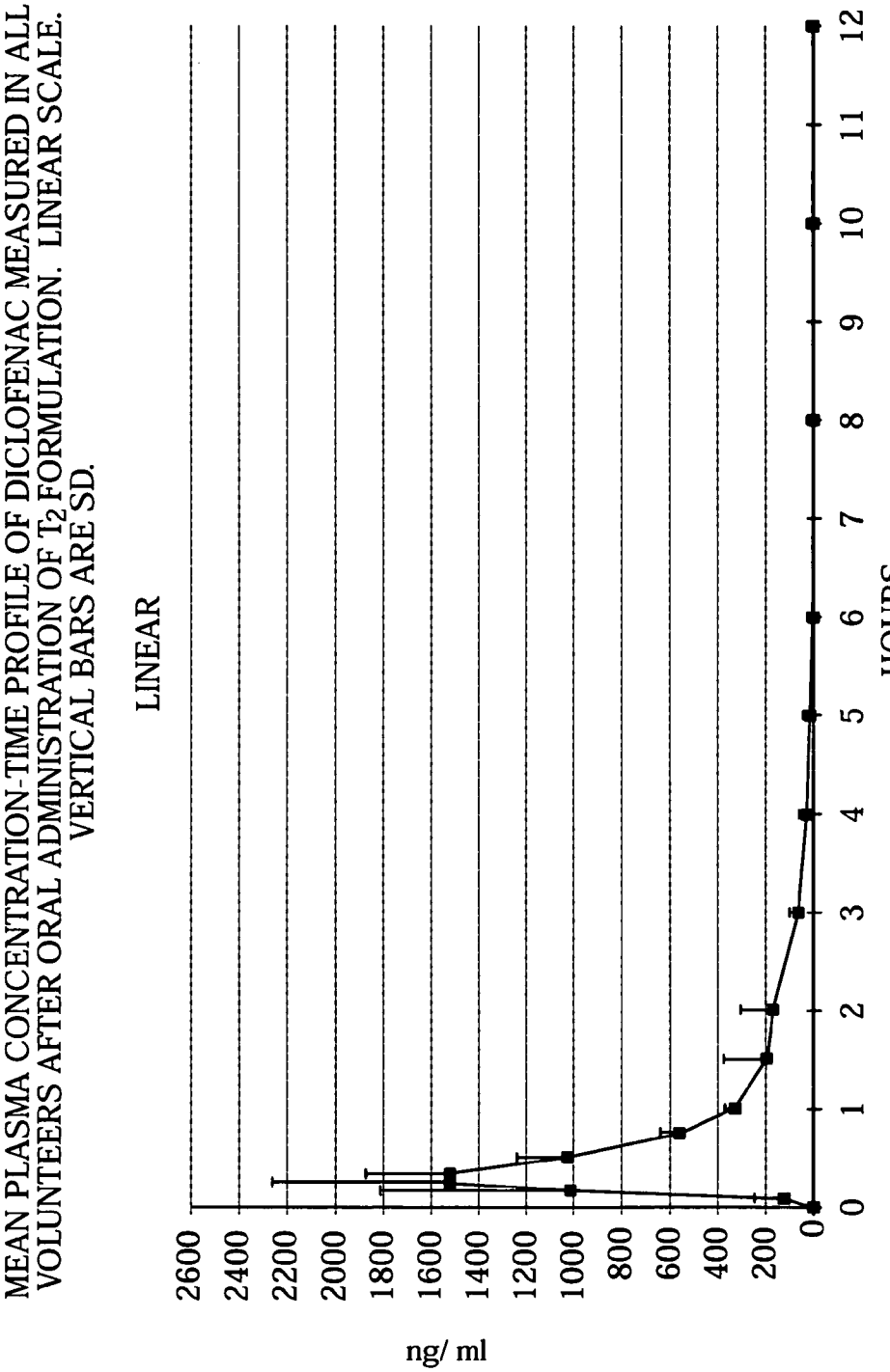

MEAN PLASMA CONCENTRATION-TIME PROFILE OF DICLOFENAC MEASURED IN ALL VOLUNTEERS AFTER ORAL ADMINISTRATION OF T2 FORMULATION. LINEAR SCALE. VERTICAL BARS ARE SD.
LINEAR
2600
2400
2200
2000
1800
1600
1400
1200
1000
800
600
400
200
0
ng/ ml
0
1
2
3
4
5
6
7
8
9
10
11
12
HOURS

FIG 8

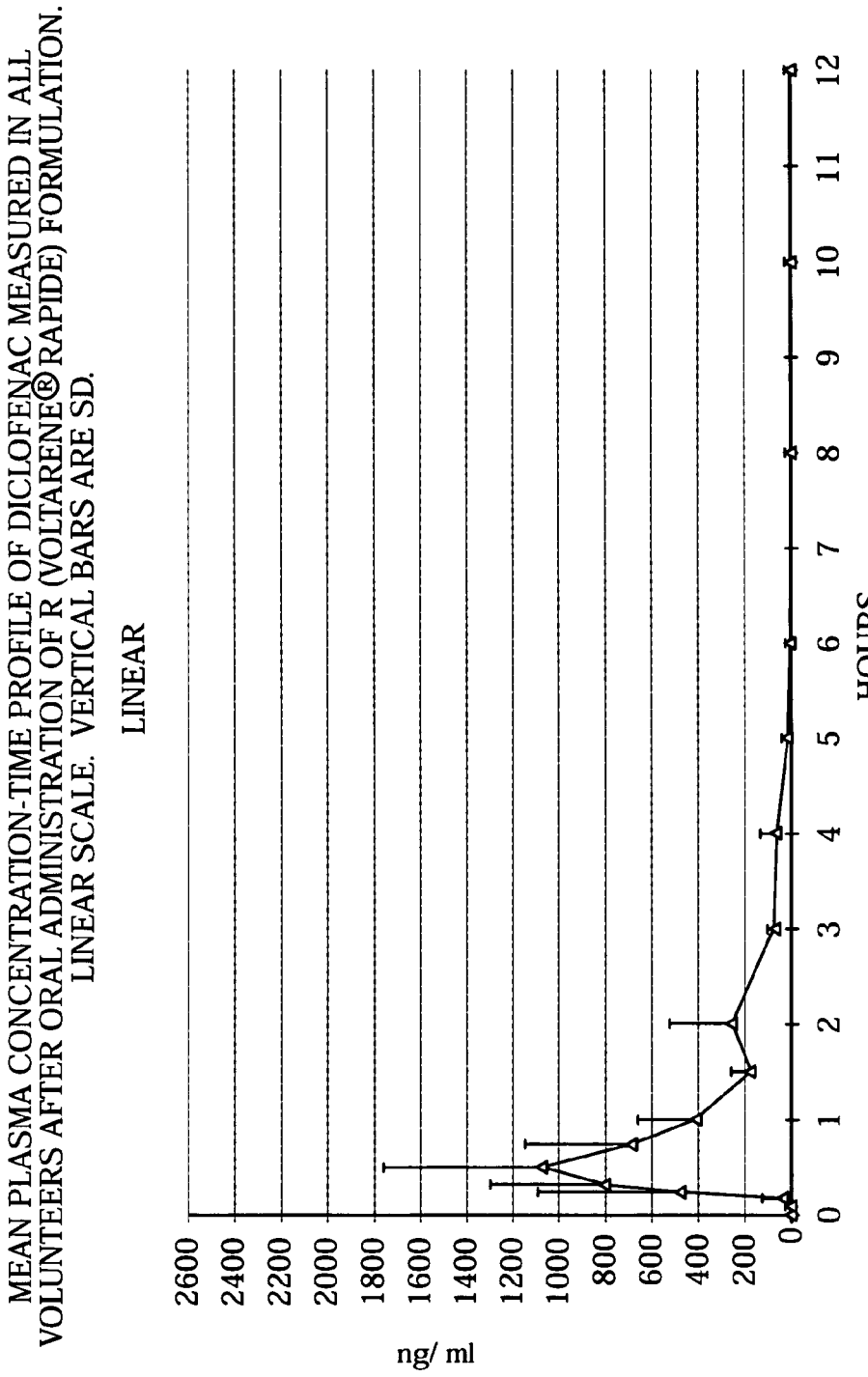

MEAN PLASMA CONCENTRATION-TIME PROFILE OF DICLOFENAC MEASURED IN ALL VOLUNTEERS AFTER ORAL ADMINISTRATION OF R (VOLTARENE® RAPIDE) FORMULATION. LINEAR SCALE. VERTICAL BARS ARE SD.
LINEAR
ng/ ml
2600
2400
2200
2000
1800
1600
1400
1200
1000
800
600
400
200
0
0
1
2
3
4
5
6
7
8
9
10
11
12
HOURS

FIG 9

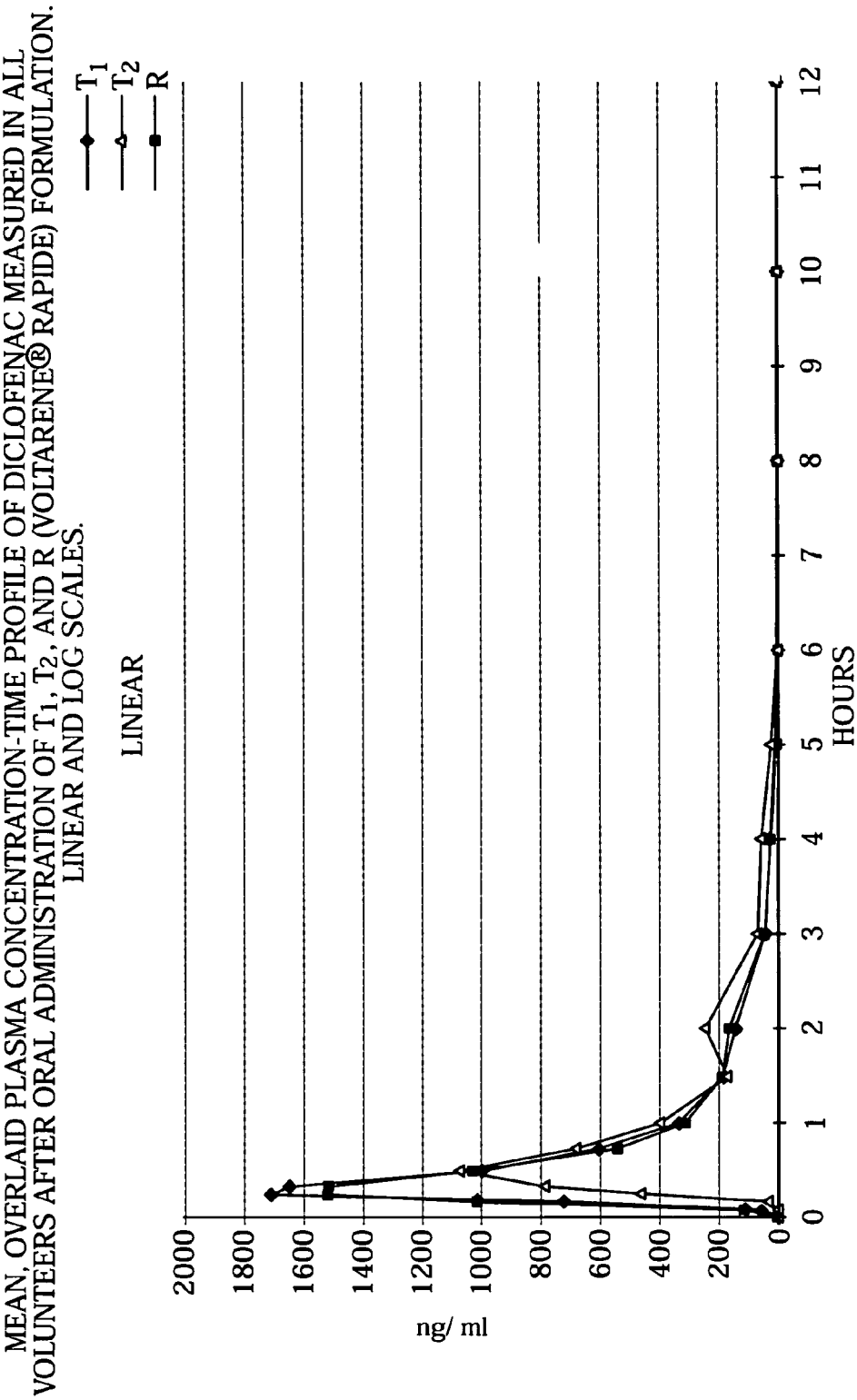

MEAN, OVERLAID PLASMA CONCENTRATION-TIME PROFILE OF DICLOFENAC MEASURED IN ALL VOLUNTEERS AFTER ORAL ADMINISTRATION OF T1, T2, AND R (VOLTARENE® RAPIDE) FORMULATION. LINEAR AND LOG SCALES.
LINEAR
T1
T2
R
2000
1800
1600
1400
1200
1000
800
600
400
200
0
ng/ ml
0
1
2
3
4
5
6
7
8
9
10
11
12
HOURS

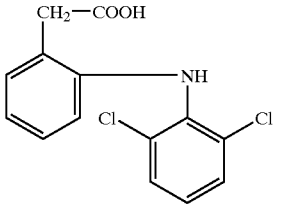
FIG 10

PHARMACEUTICAL COMPOSITIONS BASED ON DICLOFENAE

This application is a continuation-in-part of application Ser. No. 09/192,493, filed Nov. 17, 1998, now abandoned, which is a continuation of PCT/EP97/02709, filed May 15, 1997.

The present invention relates to new immediate release pharmaceutical compositions containing [(2,6-dichloro-anilino)-2-phenyl]-2-acetic acid (more commonly known as Diclofenac) in acid and/or salt form.

Diclofenac is a non-steroidal drug which was invented at the end of the sixties by A. Sallmann and R. Pfister (NL-6, 604,752 and U.S. Pat. No. 3,558,690 both to Ciba-Geigy) and whose structural formula is indicated below.



Diclofenac is widely dispensed and used owing to its well-known analgesic, anti-pyretic, anti-arthritic, anti-phlogistic and anti-rheumatic properties and it is generally taken orally in the form of normal tablets or tablets covered with coatings resistant to gastric juices, or rectally, or by injection, or topically. The possibility of taking it in the form of sweets, tablets dissolving in the mouth, drages, chewing gum or other similar pharmaceutical forms or in formulations for the extemporary preparation of Diclofenac-based aqueous solutions and/or suspensions would represent a different mode of administration which is definitely more suitable, especially for children and elderly persons.

Owing to its poor solubility in water, Diclofenac is normally used in salt form; the salts of Diclofenac customarily used are those of sodium, potassium or other alkali and alkaline earth metals, together with salts of organic nature, such as the salts of basic amino acids, such as lysine, arginine and ornithine, or other pharmacologically acceptable organic bases which have the ability to render the resulting salt soluble in water.

The pharmaceutical compositions of the Diclofenac salts for oral use are generally accompanied by side effects of not inconsiderable consequence: Diclofenac salts are in fact characterised by a particularly unpleasant and bitter taste and by the fact that they produce a sensation of strong astringency and cause an especially intense form of irritation in the buccal cavity, especially in the area of the larynx. Although the first problem has been party solved by using flavourings which are able in some manner to mask the taste, satisfactory solutions have still not been proposed for the two remaining problems.

Therefore, the pharmaceutical compositions containing Diclofenac salts still have a poor palatability which limits their adoption and possible fields of application, despite the excellent therapeutic effect with which they are associated.

A second problem connected to Diclofenac is that, when it is orally administered by means of immediate release formulations, the corresponding T_{max} (the time to the maximum plasma concentration) is usually located at about 1 hour since administration, this being of course a not completely satisfactory result when a prompt and strong analgesic/anti-pyretic effect is sought for. Furthermore, the corresponding coefficient of variation is normally in the range of 70–90%, which means that the T_{max} is strongly variable and dependent on the physical characteristics of the patient (Physicians' Desk Reference, 52 edition, 1998, pag. 1831). Attempts are therefore still being made in order to enhance the rate of absorption of Diclofenac and to provide an earlier onset of the therapeutic effect (N. Davies, K. Anderson; Clinical Pharmacokinetic of Diclofenac, Clin.Pharmacokinet., 1997, Sep. 33(3).

The object of the present invention is therefore that of providing a fully palatable formulation of Diclofenac which is able to generate a more rapid, uniform and foreseeable release of the active principle if compared to the compositions known in the art and presently available on the market. For the purposes of the present invention T_{max} means the time to the maximum plasma concentration whereas C_{max} is the maximum plasma concentration of the active principle, namely Diclofenac. It has now been found that, by adding alkali metal bicarbonates or mixtures thereof to the Diclofenac in its acid and/or salt form, in amounts of from 20 to 80 % by weight based on the acid-form of Diclofenac, pharmaceutical compositions can be obtained which are substantially free from the side effects mentioned above. The first object of the present invention is therefore represented by a pharmaceutical formulation for oral use containing Diclofenac ill acid and/or Salt form together with alkali metal bicarbonates or mixtures thereof and customary excipients and adjuvants, wherein said alkali metal bicarbonates are present in amounts of from 20 to 80% by weight based on the weight of Diclofenac. It has in fact been surprisingly demonstrated that the use of alkali metal bicarbonates in the above-mentioned ratio permits to achieve constant, reproducible and foreseeable blood levels of the active ingredient, with the consequent indisputable advantages from the therapeutic point of view; furthermore, it has also been found that the combined use of Diclofenac together with alkali metal bicarbonates yields Diclofenac-based pharmaceutical compositions in which the active ingredient is released more rapidly compared with normal formulations, bringing about higher blood levels and therefore a more immediate therapeutic effect; finally the so-obtained immediate release formulations are substantially palatable and free from aftertaste.

According to the preferred embodiment of the present invention, the amount of alkali metal bicarbonates to be added is comprised between 40 and 80% by weight, based on the weight of the acid-form Diclofenac, whereas the alkali metal bicarbonates are selected from sodium and/or potassium bicarbonates, Diclofenac being normally present in the form of its sodium and/or potassium salts.

It has also been found, and forms a second subject of the present invention, that the addition of flavouring substances selected from mint, aniseed, ammonium glycyrrhizinate and mixtures thereof to the compositions containing the Diclofenac salts and alkali metal bicarbonates produces a synergistic effect which completely eliminates all the above-mentioned palatability/astringency effects, providing pharmaceutical compositions which are entirely palatable (and/or drinkable in the case of those used for the preparation of solutions and/or suspensions) and free from aftertaste.

The flavouring substances may be used as such or supported on inert materials, for example maltodextrin, in order to obtain a better distribution of the granulates and to facilitate excellent dispersibility of the flavouring in solu-

tion. Preferably, they are absorbed on maltodextrin with a power of 1 to 2000 and 1 to 1000.

The amount of flavouring substances in its pure form is also preferably from ⅕ to 3 times the weight of the acid-form Diclofenac.

These flavouring substances are used in the implementation of the present invention without altering their organoleptic properties and without depriving them of their intrinsic qualities of flavourings which are liposoluble and generally oily in the pure state.

As it will be clear from the examples, the immediate release formulations for oral use of the present invention containing from 10 to 60 mg of Diclofenac in acid and/or salt form together with alkali metal bicarbonates or mixtures thereof in amounts of from 20 to 80% by weight based on the weight of Diclofenac permit to generate in human patients an average C_{max} of Diclofenac comprised between 400 and 2500 ng/ml independently on the age, sex or weight of the patients themselves.

Secondly, the formulations according to the present invention permit to obtain in humans an average T_{max} of Diclofenac after 5÷30 minutes since administration, generally 13÷27, independently on the amount of Diclofenac contained therein and also independently on the age, sex, weight of the patient.

Furthermore, the T_{max} of the formulations of the present invention show a coefficient of variation which is about 44–86% lower than the presently marketed formulations; this is evidently an extremely important result from the clinical point of view as it is now possible to have a therapeutical effect of Diclofenac which is foreseable, reproducible and independent on the sex, weight and health conditions of the patient.

Thus, the presently claimed Diclofenac-based formulations permit to achieve a higher C_{max} in a shorter T_{max} and with a lower coefficient of variation if compared to the formulations available on the market, with therapeutical advantages which do not need to be commented.

According to the best mode for carrying out the present invention the pharmaceutical formulations will contain from 10 to 60 mg/dose of diclofenac in its potassium or sodium salt form together with 40 to 80% by weight of potassium or sodium bicarbonate based on the weight of Diclofenac in its acid form, together with the usual excipients and adjuvants; even more preferably they will packaged as:

- a sachet or tablet formulation containing 50 mg of Diclofenac potassium salt and 22 mg of potassium bicarbonate or 50 mg of Diclofenac sodium salt and 19 mg of sodium bicarbonate;
- a sachet or tablet formulation containing 12.5 mg of Diclofenac sodium salt and 5.5 mg of potassium bicarbonate or 25 mg of Diclofenac sodium salt and 11 mg potassium bicarbonate.

It will be by the way evident to any skilled in this art that the present formulations can also be used as immediate release layers of multilayered release pharmaceutical formulations containing Diclofenac as one of the active ingredients; said formulations are therefore a further object of the present invention.

The following Examples are given purely by way of non-limiting illustration.

Example 1 - Composition dissolving instantly in water

Active ingredients	
1) Diclofenac potassium salt*	50 mg
2) Potassium bicarbonate:	22 mg
3) Mint flavouring on maltodextrin(1:2000)**:	60 mg
4) Aniseed flavouring on maltodextrin (1:1000)***:	104 mg
Excipients and adjuvants	
5) Saccharin:	4 mg
6) Aspartame:	10 mg
7) Mannitol:	50 mg
8) Saccharose**** *q.s.:	2 g

*If it is desired to prepare compositions based on Diclofenac sodium salt, it is advantageous to use sodium bicarbonate in a quantity of approximately 38% by weight based on the weight of the Diclofenac sodium salt present. Sodium carbonate may also be added to the sodium bicarbonate, maintaining the following optimum proportions: 27% of sodium bicarbonate and 4–5% of sodium carbonate, always based on the amount by weight of Diclofenac sodium salt present.

**The title of the pure mint essence, as obtained according to the Dean-Stark method, is of 18% by weight; the related amount is therefore in this case of 10.8 mg.

***The title of the pure anise essence, as obtained according to the Dean-Stark method, is of 14.5% by weight, the related amount is therefore in this case of 16 mg.

****The presence of saccharose is not strictly necessary; in its absence, a composition having a very limited granulate content is obtained which is perfectly soluble in contact with water. In that case, nothing is changed from the point of view of tolerability in contact with the mucosa and from the point of view of the palatability of the drinkable solution.

Preparation

Components **1**, **2**, **5**, **6** and **7** are mixed in a suitable mixer, and the mixture so obtained is wetted with 95% ethanol. Granulation is carried out with a 66 mm mesh and the granulate is preferably dried in a current of air.

Components **3**, **4** and **8**, which have already been granulated using a mesh of the same granulometry, are then added and the whole is mixed.

The mixture is then introduced into a metering machine filling packets or similar containers.

Example 2 - Tablet for dissolving in the mouth

Active ingredients	
1) Diclofenac potassium sait*:	50 mg
2) Potassium bicarbonate:	35 mg
3) Mint flavouring on maltodextrin** (1:2000) + gum arabic (E 414):	50 mg
4) Aniseed flavouring (1:1000) on maltodextrin*** + silicon dioxide (E 551):	120 mg
Excipients and adjuvants	
5) Saccharin:	50 mg
6) Aspartame:	12 mg
7) Mannitol:	20 mg
8) Saccharose****:	300 mg

*to**** see Example 1

Example 3 - Gum tablet

Active ingredients	
1) Diclofenac potassium salt*:	50 mg
2) Potassium bicarbonate:	35 mg
3) Mint flavouring on maltodextrin**:	30 mg
4) Aniseed flavouring on maltodextrin***:	80 mg
Excipients and adjuvants	
5) Mannitol:	30 mg

-continued

6) Menthol:	0.01 mg
7) Gum base:	600 mg
8) Sorbitol:	700 mg
9) Saccharin:	3 mg
10) Hydroxypropylmethylcellulose:	33 mg
11) Colouring agent:	7 mg

*to*** see Example 1

Example 4

Comparative Test

The packaged composition containing 50 mg of Diclofenac potassium of Example 1 (formulation C) was subjected to a pharmacokinetic test for comparison with a similar composition not containing alkali metal carbonates and bicarbonates (formulation B), and with a second composition in tablet form (formulation A) produced by Ciba-Geigy (Voltaren Rapid®), also in this case not containing alkali metal carbonates and bicarbonates, both formulations A and B containing 50 mg of Diclofenac potassium.

This comparative evaluation was carried out on the same 6 healthy volunteers in accordance with the experimental plan described hereinafter.

Experimental scheme: Single-dose study using three methods in randomised cross-over with a wash-out of three days.

Sampling times: 0 h (before administration), 5 min, 10 min, 30 min, 45 min, 1 h, 1.5 h, 2 h, 3 h, 4 h, 6 h, 8 h, after each administration.

Blood sample treatment: 8MI in heparinised test tubes, centrifugation for 15 min at 1500 rev/min, subdivided into two fractions and subsequently frozen at −20° C.

Times: wash-out of two days between treatments.

Determination method: HPLC, with internal standard, sensitivity 10 ng/ml.

Analysis Method

Column: Nova Pak C18, 3.9×150 mm, 4 μm Waters S.p.A.—Vimodrone, Italy.

Eluant: NaH2PO4 0.01 M+0.1% TEA, pH 3.0 (H3P04)/acetonitrile, 60/40.

Flow: 1.2 ml/min

Detection: UV/275 nm

Temperature: 30° C.

Injection: 50 al

Analysis time: 16 min.

Sample Preparation

10 al of the internal standard methanolic solution, and flufenamic acid (corresponding to 1320 ng) are added to 1 ml of defrosted plasma in 10 ml glass test tubes. The tubes are agitated in a Vortex mixer for 1 minute. 0.5 ml of a 0.5N HCl/1N NaCl solution is added. The whole is agitated in a Vortex mixer for 1 minute. 6 ml of a 95/5 n-hexane/isopropanol solution are added.

The mixture is then agitated in the Vortex mixer for a further 15 minutes. Centrifugation is carried out at 3000 rev/min for 15 minutes and the organic phase is transferred to fresh 10 ml glass test tubes and evaporated to dryness in a centrifugal evaporator under vacuum at ambient temperature. The whole is taken up in 200 al of a 70/30 acetonitrile/water solution, and the precipitate is dissolved under ultrasound for 2 minutes.

FIGS. **1**, **2** and **3** show the concentrations of Diclofenac in the blood of the six volunteers as regards formulations A, B (Ciba-Geigy comparative formulations) and C (formulation corresponding to the composition of Example 1), respectively. As will be appreciated, the blood concentration of the formulation of the present invention has, compared with the comparative formulations, a more constant and uniform pattern. This characteristic is also found in FIGS. **4**, **5** and **6** which show the average values corresponding to the blood levels of the six volunteers together with the corresponding standard deviation.

The result is clear and surprising: compared with the sample compositions, the compositions of the present invention permit constant, reproducible and foreseeable blood levels of the active ingredient, irrespective of the characteristics of the volunteer (weight, age, etc), with the consequent indisputable advantages from the therapeutic point of view.

Finally, FIG. **7** shows, by comparison, the graphs relating to the average values of the six volunteers (that is to say, the preceding FIGS. **4**, **5** and **6**); as will be noted, the formulation of the present invention permits, in addition to the advantages already mentioned, the attainment of a blood peak higher than that of the other formulations.

Example 5 - Two layered tablet (fast and slow release)

Fast release layer

1) Diclofenac potassium salt:	15 mg
2) Potassium bicarbonate:	30 mg
3) Lactose:	13.2 mg
4) Maize starch (intragranular):	6 mg
5) Methyl cellulose:	0.12 mg
6) Sodium laurylsulfate:	0.06 mg
7) Maize starch (extragranular):	9 mg
8) Crospovidone:	0.6 mg
9) Sodium carboxtmethylstarch:	1.5 mg
10) Magnesium stearate:	2.7 mg
11) Colloidal silicon dioxide:	0.6 mg

Slow release layer

1) Diclofenac potassium salt:	70 mg
2) Potassium bicarbonate:	30.8 mg
3) Lactose:	32.2 mg
4) Polyvinylpyrrolidone:	1.16 mg
5) Hydrpxypropylmethylcellulose:	70 mg
6) Magnesium stearate:	0.84 mg
7) Colloidal silicon dioxide:	0.21 mg
8) Talc:	3.92 mg
9) Polyethylene glycol:	0.56 mg

Example 6 - Drops

1) Diclofenac potassium salt:	75 g
2) Methyl p-oxybenzoate:	2.7 g
3) Propyl p-oxybenzoate:	0.3 g
4) Aspartame:	37.5 g
5) Potassium bicarbonate:	37.5 g
6) Glycerol:	300 g
7) Ethyl alcool:	450 g
8) Water q.s.:	1500 g

Possible modifications:

a) Addition of sodium metabisulfite (0.06%)
b) Addition of sodium metabisulfite (0.06%)
Mint flavouring (1.25%)
Strawberry flavouring (0.75%)

Example 7 - Drops

1) Diclofenac potassium salt:	37.5 g
2) Methyl p-oxybenzoate:	2.7 g
3) Propyl p-oxybenzoate:	0.3 g
4) Aspartame:	37.5 g
5) Potassium bicarbonate:	18.75 g
6) Saccharin:	6.0 g

-continued

7) Glycerol:	300 g
8) Ethyl alcool:	450 g
9) Water q.s.:	1500 g
Possible modifications:	
a) Addition of sodium metabisulfite (0.03%)	
b) Addition of sodium metabisulfite (0.03%)	
Mint flavouring (1.25%)	
Strawberry flavouring (0.75%)	

Example 8 - Mouthwash

1) Diclofenac potassium salt:	0.75 g
2) Glycerol:	50 g
3) Sorbitol:	12 g
4) Saccharin:	0.5 g
5) Aspartame:	1.0 g
6) Methyl p-oxybenzoate:	0.5 g
7) Propyl p-oxybenzoate:	0.1 g
8) Mint flavouring:	1.0 g
9) Ethyl alcool:	100 g
10) Potassium bicarbonate:	0.33 g
11) Water q.s.:	500 ml

Example 9 - Gum-paste

1) Diclofenac potassium salt:	5.0 g
2) Glycerol:	630 g
3) Sodium benzoate:	5.0 g
4) Silica (Wessalon S ® - Degussa):	120 g
5) Silica (Siddent 9 ® - Degussa):	80 g
6) Cellulose gum:	3.0 g
7) Polyethylenglycol 600:	30 g
8) Sodium lauroyl sarcosinate (or sodium lauryl sulfate):	60 g
9) Mint flavouring:	10 g
10) Sodium saccharin:	1.0 g
11) Aspartame:	3.0 g
12) Potassium bicarbonate:	2.2 g
13) Water q.s.:	1 kg

Example 10 - Tooth-paste

1) Diclofenac potassium salt:	5.0 g
2) Glycerol:	630 g
3) Sodium benzoate:	5.0 g
4) Silica (Wessalon S ® - Degussa):	20 g
5) Silica (Siddent 9 ® - Degussa):	80 g
6) Cellulose gum:	3.0 g
7) Polyethylenglycol 600:	30 g
8) Sodium lauroyl sarcosinate (or sodium lauryl sulfate):	60 g
9) Mint flavouring:	10 g
10) Sodium saccharin:	1.0 g
11) Aspartame:	3.0 g
12) NaF:	1.0 g
13) Na_2FPO_3:	4.0 g
14) Potassium bicarbonate:	2.2 g
15) Water q.s.:	1 kg

Example 11 - Tablet

1) Diclofenac potassium salt:	50 mg
2) Mannitol:	50 mg
3) Potassium bicarbonate:	22 mg
4) Maize starch (intragranular):	10 mg
5) Methyl cellulose:	0.2 mg
6) Sodium laurylsulfate:	0.1 mg
7) Maize starch (extragranular):	15 mg
8) Crospovidone:	1.0 mg
9) Sodium carboxymethylstarch:	2.5 mg
10) Magnesium stearate:	4.5 mg
11) Colloidal silicon dioxide:	10 mg

Example 12

Comparative Test

In the present experiment a sachet formulation containing 50 mg of Diclofenac potassium was compared to a bioequivalent sugar coated fast release tablet also containing 50 mg of Diclofenac potassium, produced and marketed in Italy by Novartis as Cataflam®.

The sachet formulation according to the present invention had the following composition:

1) Diclofenac potassium salt:	50 mg
2) Potassium bicarbonate:	22 mg
3) Mint flavour:	50 mg
4) Anice flavour	100 mg
5) Saccharin sodium:	4 mg
6) Aspartame:	10 mg
7) Mannitol:	50 mg
8) Sucrose sugar crystals:	1714 g

The above test formulation and the Cataflam® formulation were administered as a single dose to 24 healty volunteers of both sexes. The pharmacokinetic parameters obtained with the two different formulations are reported in table 1 and in FIG. **5**. As it will be easily appreciated, the rate of absorption was considerably faster with the sachet formulation of the present invention than with Cataflam®D, the sachet formulation having a higher average C_{max} (2213 vs 1071 ng/ml) and a shorter average T_{max} (0.228 vs 0.885 hours); furthermore, the T_{max} of the sachet formulation shows a coefficient of variation lower than the reference formulation (16% vs 97%), this being an extremely important result from the clinical point of view regarding the healing of the pain in terms of quick time and repeteability inter-subjects in order to reach the C_{max}.

Example 13

Comparative Test

Following to the excellent results obtained in example 12, two tablet formulations containing 12.5 or 25 mg of Diclofenac sodium salt and potassium bicarbonate (in the same weight ratio) have been prepared.

The tablet formulations had the following composition (in mg):

Cores		
Diclofenac sodium	12.5	25
Mannitol	25	50
Lactose monohydrate	23.75	47.5
Potassium bicarbonate	5.5	11
Maize starch	22.5	45
Methylcellulose	0.075	0.15
Sodium laurylsulphate	0.125	0.25
Crospovidone	3	6
Ultramyl	5	10
Coloidal silica	0.55	1.1
Cellulose microcrystalline	0.5	1
Magnesium stearate	1.5	3
Purified water q.s.	100	200

-continued

	Coating	
Opadry OY-35009 red	2	4
Macrogol 400	0.25	0.5

A four-way comparative bioavailability study was carried out on 18 healty volunteers of both sexes in order to evaluate the in vivo results of the pharmaokinetic profiles of the present formulations if compared to those of bioequivalent fast release formulations such as Cataflam® (25 mg of Diclofenac potassium) and Voltarol® (50 mg of Diclofenac sodium), both by Novartis. The results, which are summarized in FIG. **6**, indicate that T_{max} is prompter with the present formulations (T1=26 min, T2=24.6 min vs R1 71.4 min and R2= 40.8 min) and that C_{max} is higher (T1=847 ng/ml and T2=861 ng/ml vs R1= 452 ng/ml and R2=703 ng/ml); furthermore, the T_{max} of both present formulations shows a coefficient of variation lower than reference formulations (T1=46% and T2=49% vs R1=87% and R=96%).

Example 14

Comparative Test

A further comparative test was carried out on immediate release formulations according to the present invention, containing 50 mg of Diclofenac potassium and 22 mg of potassium bicarbonate, manufactured with different that is, respectively: T1=wet granulation using alcohol, T2=dry granulation by direct compression. The composition in mg of the two formulations is herebelow reported:

Diclofenac potassium	50	50
Potassium bicarbonate	22	22
Mannitol/pearlitol 400 DC	119.9	
Mannitol EP cf		50
Maize starch		25
Methocel A4C		0.2
Sodium laurylsulphate	0.1	0.1
Polyplasdone XL	6	1
Ultramyl		2.5
Magnesium stearate	2	4.5
Silicium aerosil		1
Core mass	200	156.3

A comparative bio availability study was carried out on 6 healty volunteers of both sexes in order to evaluate the in vivo results of the pharmaokinetic profiles of the present formulations if compared to those of a bioequivalent fast release formulation such Voltarene Rapid® (50 mg of Diclofenac potassium), both by Novartis. The results, which are reported in FIGS. **7**–**10** are also in this case excellent: the T_{max} is in fact prompter with the present formulations (T1=18.6 min, T2=16.8 min vs R1=40.8 min) and the C_{max} is higher (T1=1878.3 ng/ml and T2=1744.8 ng/ml vs R1=1307 ng/ml); furthermore, also in this case the T_{max} of both present formulations shows a coefficient of variation lower than reference formulation (T1=12.9% and T2=25% vs R1=95.6%).

TABLE 1

Pharmacokinetic parameters for two different diclofenac formulations: test (Diclofenac potassium and reference (Diclofenac potassium salt sugar coated tablets)

	t_{max} (h)		C_{max} (ng/mL)		$t_{1/2}$ (h)		AUC_{0-t} (ng · mL^{-1} · h)	
Vol. no.	Test	Ref.	Test	Ref.	Test	Ref.	Test	Ref.
Vol. 1	0.250	0.500	1573.000	1186.211	1.505	0.939	1024.511	885.549
Vol. 2	0.250	4.000	2382.368	965.100	0.875	1.358	1653.124	2092.036
Vol. 3	0.184	1.000	2614.655	1352.400	0.796	1.610	1687.529	1763.484
Vol. 4	0.250	3.000	2404.848	735.454	0.996	1.132	1881.944	1834.958
Vol. 5	0.250	0.500	2971.457	1405.000	1.667	1.903	1819.756	1687.075
Vol. 6	0.250	0.750	2158.700	1351.500	0.843	0.650	1197.716	1091.996
Vol. 7	0.250	0.750	1739.200	1741.717	0.596	0.658	1448.713	1301.887
Vol. 8	0.250	0.500	1715.350	534.300	0.818	1.111	991.864	1126.414
Vol. 9	0.250	0.750	444.112	747.800	0.787	1.188	669.084	886.300
Vol. 10	0.267	0.750	2350.100	1110.400	0.960	1.070	1327.808	1020.286
Vol. 11	0.167	0.500	1867.200	1465.502	1.141	0.762	1337.821	892.870
Vol. 12	0.167	0.500	4273.026	1432.200	1.052	0.697	1703.655	1139.003
Vol. 13	0.250	0.500	2097.089	1155.371	1.313	1.198	1486.526	1233.531
Vol. 14	0.167	0.250	2242.684	967.795	0.997	0.837	987.522	927.726
Vol. 15	0.184	0.500	2040.247	1129.957	0.724	0.804	1213.725	1040.424
Vol. 16	0.250	0.750	2143.692	818.200	0.560	1.199	1186.603	1250.221
Vol. 17	0.250	1.500	1527.845	480.900	2.752	1.309	958.821	978.797
Vol. 18	0.250	1.000	1859.608	666.500	1.630	1.383	1131.413	933.008
Vol. 19	0.250	0.750	1537.508	770.100	1.726	1.137	980.348	906.275
Vol. 20	0.250	0.250	1956.004	655.100	0.853	0.883	1309.289	1036.836
Vol. 21	0.250	0.500	3551.360	2421.060	1.322	1.233	2147.217	1639.619
Vol. 22	0.167	0.500	2464.978	1274.648	0.611	0.624	1038.817	816.924
Vol. 23	0.167	0.750	2304.351	453.500	2.066	0.862	1161.414	1049.327
Vol. 24	0.250	0.500	2901.504	894.337	0.970	1.279	1645.384	1086.512
Mean	0.228	0.885	2213.370	1071.461	1.148	1.076	1332.942	1192.544
SD	0.037	0.860	743.099	450.780	0.523	0.320	358.048	350.116
CV %	16.300	97.091	33.573	42.072	45.557	29.700	26.862	29.359
Min.	0.167	0.250	444.112	453.500	0.560	0.624	669.084	816.924
Max.	0.267	4.000	4273.026	2421.060	2.752	1.903	2147.217	2092.036

TABLE 1-continued

Pharmacokinetic parameters for two different diclofenac formulations: test (Diclofenac potassium and reference (Diclofenac potassium salt sugar coated tablets)

Geom. Mean	0.225	0.692	2070.719	987.180	1.056	1.032	1287.195	1150.713
Median	0.250	0.625	2151.196	1039.098	0.983	1.122	1261.507	1067.920

	$AUC_{0-\infty}$ ($ng \cdot mL^{-1} \cdot h$)		C_t		$C_{max}/AUC_{0-\infty}$ (h^{-1})		AUC extrapolated (%)	
Vol. no.	Test	Ref.	Test	Ref.	Test	Ref.	Test	Ref.
Vol. 1	1050.137	910.868	11.800	18.700	1.498	1.302	2.37	0.00
Vol. 2	1693.172	2092.036	31.700	13.500	1.407	0.461	1.82	1.38
Vol. 3	1718.755	1788.111	27.200	10.600	1.521	0.756	0.83	1.15
Vol. 4	1897.754	1856.346	11.000	13.100	1.267	0.396	1.39	1.88
Vol. 5	1845.486	1719.478	10.700	11.800	1.610	0.817	1.56	1.90
Vol. 6	1216.693	1113.146	15.600	22.500	1.774	1.214	2.50	1.79
Vol. 7	1485.867	1325.661	43.200	25.000	1.170	1.314	1.46	1.78
Vol. 8	1006.522	1146.775	12.400	12.700	1.704	0.466	3.08	2.75
Vol. 9	690.354	911.329	18.700	14.600	0.643	0.821	1.74	1.80
Vol. 10	1351.357	1038.971	17.000	12.100	1.739	1.069	3.01	3.01
Vol. 11	1379.311	920.579	25.200	25.200	1.354	1.592	1.62	2.03
Vol. 12	1731.709	1162.638	18.500	23.500	2.468	1.232	1.26	1.56
Vol. 13	1505.454	1253.088	10.000	11.300	1.393	0.922	2.58	2.26
Vol. 14	1013.665	949.163	18.200	17.700	2.212	1.020	1.91	2.86
Vol. 15	1237.399	1071.029	22.700	26.400	1.649	1.055	1.33	1.58
Vol. 16	1202.653	1270.280	19.900	11.600	1.782	0.644	4.16	2.80
Vol. 17	1000.433	1006.986	10.500	14.900	1.527	0.478	5.51	2.26
Vol. 18	1197.411	954.597	28.100	10.800	1.553	0.698	2.57	2.11
Vol. 19	1006.229	925.835	10.400	11.900	1.528	0.832	2.03	2.02
Vol. 20	1336.472	1058.242	22.400	16.800	1.464	0.619	1.19	1.07
Vol. 21	2173.030	1657.372	13.500	10.000	1.634	1.461	1.75	1.68
Vol. 22	1057.293	830.908	21.000	15.500	2.331	1.534	3.13	1.80
Vol. 23	1198.950	1068.588	12.600	15.500	1.922	0.424	2.19	1.94
Vol. 24	1682.290	1108.024	26.400	11.700	1.725	0.807	2.10	1.78
Mean	1361.600	1214.169	19.113	15.725	1.620	0.914	2.213	1.883
SD	358.359	348.108	8.244	5.160	0.377	0.365	1.035	0.641
CV %	26.319	28.671	43.134	32.812	23.277	39.991	46.795	34.056
Min.	690.354	830.908	10.000	10.000	0.643	0.396	0.833	0.000
Max.	2173.030	2092.036	43.200	26.400	2.468	1.592	5.512	3.010
Geom. Mean	1316.580	1173.325	17.609	15.011	1.573	0.841	2.023	//
Median	1286.936	1089.527	18.350	14.050	1.582	0.827	1.974	1.843

What is claimed is:

1. A method for obtaining an average T_{max} of diclofenac in a human patient between 5 and 30 minutes after administering said diclofenac to said patient, said average T_{max} having a coefficient of variation (CV%) less than about 70%, comprising orally administering a diclofenac formulation to said patient, wherein said diclofenac formulation comprises diclofenac in acid and/or salt form together with an alkali metal bicarbonate selected from the group consisting of sodium bicarbonate, potassium bicarbonate and mixtures thereof, wherein said alkali metal bicarbonate is present in an amount of from about 20 to about 80% by weight based on the weight of said diclofenac, wherein said diclofenac formulation further contains a flavoring substance selected from the group consisting of mint, aniseed, ammonium glycyrrhizinate and mixtures thereof whereby palatability and astringency effects are eliminated, and wherein said diclofenac formulation is selected from:

a. a powder formulation dissolved or dispersed in water; and

b. a fast release layer present in a two layered diclofenac tablet that comprises a slow release layer and a fast release layer.

2. The method according to of claim **1** where said average T_{max} is reached 13–27 minutes after said administration.

3. A The method according to of claim **1** wherein said alkali metal bicarbonate is present in an amount of from about 40 to about 80% by weight based on the weight of said diclofenac.

4. The method of claim **1** wherein said diclofenac formulation comprises from about 10 to about 60 mg. of diclofenac in its potassium salt form.

5. The method of claim **1** wherein said diclofenac formulation comprises from about 10 to about 60 mg. of diclofenac in its sodium salt form.

6. The method of claim **1** wherein said alkali metal bicarbonate is sodium bicarbonate.

7. The method of claim **1** wherein said alkali metal bicarbonate is potassium bicarbonate.

8. The method of claim **1** wherein said diclofenac formulation is said powder formulation.

9. The method of claim **1** wherein said diclofenac formulation is said fast release layer.

10. The method of claim **1** wherein said diclofenac formulation is said powder formulation, and said diclofenac formulation comprises about 50 mg. of diclofenac potassium salt.

11. The method of claim **1** wherein said diclofenac formulation is said fast release layer, said diclofenac formulation comprises about 15 mg. of diclofenac potassium salt, and said slow release layer comprises about 70 mg. of diclofenac potassium salt.

12. The method of claim **1** wherein said diclofenac formulation comprises about 50 mg. of diclofenac potassium salt and from about 22 to about 24 mg. of potassium bicarbonate.

13. The method of claim **1** wherein said diclofenac formulation comprises about 50 mg. of diclofenac and said administration achieves an average C_{max} of from about 1700 to about 2300 ng/ml.

14. A method of treating a human patient with diclofenac comprising orally administering a diclofenac formulation to said patient, wherein said diclofenac formulation comprises diclofenac in acid and/or salt form together with one or more alkali metal carbonates or bicarbonates, wherein said one or more alkali metal carbonates or bicarbonates is present in an amount of greater than about 20% by weight based on the weight of said diclofenac, and wherein said diclofenac formulation is selected from:

a. a powder formulation dissolved or dispersed in water; and

b. a fast release layer present in a two layered diclofenac tablet that comprises a slow release layer and a fast release layer.

15. The method of claim **14** wherein an average T_{max} of diclofenac is reached between 5 and 30 minutes after orally administering said diclofenac formulation.

16. The method of claim **14** wherein an average T_{max} of diclofenac is reached between 5 and 30 minutes after orally administering said diclofenac formulation, said average T_{max} having a coefficient of variation (CV%) less than about 70%.

17. The method of claim **14** wherein said diclofenac formulation comprises about 50 mg. of diclofenac and said administering achieves an average C_{max} of from about 1700 to about 2300 ng/ml.

18. The method of claim **14** wherein said diclofenac formulation comprises from about 10 to about 60 mg. of diclofenac in its potassium salt form.

19. The method of claim **14** wherein said diclofenac formulation comprises from about 10 to about 60 mg. of diclofenac in its sodium salt form.

20. The method of claim **14** wherein said one or more alkali metal carbonates or bicarbonates is present in an amount of from about 40 to about 80% by weight based on the weight of diclofenac.

21. The method of claim **14** wherein said diclofenac formulation comprises sodium bicarbonate.

22. The method of claim **14** wherein said diclofenac formulation comprises potassium bicarbonate.

23. The method of claim **14** wherein said diclofenac formulation is said powder formulation.

24. The method of claim **14** wherein said diclofenac formulation is said fast release layer.

25. The method of claim **14** wherein said diclofenac formulation is said powder formulation, and said diclofenac formulation comprises about 50 mg. of diclofenac potassium salt.

26. The method of claim **14** wherein said diclofenac formulation is said fast release layer, said diclofenac formulation comprises about 15 mg. of diclofenac potassium salt, and said slow release layer comprises about 70 mg. of diclofenac potassium salt.

27. The method of claim **14** wherein said diclofenac formulation comprises about 50 mg. of diclofenac potassium salt and from about 22 to about 24 mg. of potassium bicarbonate.

28. A method for obtaining an average T_{max} of diclofenac in a human patient between 5 and 30 minutes after administration comprising orally administering a diclofenac formulation to said patient, wherein said diclofenac formulation comprises diclofenac in acid and/or salt form, and wherein said diclofenac formulation is selected from:

a. a powder formulation dissolved or dispersed in water; and

b. a fast release layer present in a two layered diclofenac tablet that comprises a slow release layer and a fast release layer.

29. The method of claim **28** wherein said average T_{max} has a coefficient of variation (CV%) less than about 70%.

30. The method of claim **28** wherein said average T_{max} is reached 13–27 minutes after administration.

31. The method of claim **28** wherein said diclofenac formulation comprises about 50 mg. of diclofenac and said administration achieves an average C_{max} of from about 1700 to about 2300 ng/ml.

32. The method of claim **28** wherein said diclofenac formulation is said powder formulation.

33. The method of claim **28** wherein said diclofenac formulation is said fast release layer.

34. A method for obtaining an average T_{max} of diclofenac in a human patient between 5 and 30 minutes after administration comprising orally administering a diclofenac formulation to said patient, wherein said diclofenac formulation comprises diclofenac in acid and/or salt form and means for enhancing said average T_{max} of said diclofenac, and wherein said diclofenac formulation is selected from:

a. a powder formulation dissolved or dispersed in water; and

b. a fast release layer present in a two layered diclofenac tablet that comprises a slow release layer and a fast release layer.

35. The method of claim **34** wherein said average T_{max} has a coefficient of variation (CV%) less than about 70%.

36. The method of claim **34** wherein said T_{max} of diclofenac is reached 13–27 minutes after administration.

37. The method of claim **34** wherein said diclofenac formulation comprises about 50 mg. of diclofenac and said administration achieves an average C_{max} of from about 1700 to about 2300 ng/ml.

38. The method of claim **34** wherein said means for enhancing said average T_{max} of said diclofenac comprises one or more alkali metal carbonates or bicarbonates.

39. The method of claim **34** wherein said means for enhancing said average T_{max} of said diclofenac comprises one or more alkali metal carbonates or bicarbonates in an amount of from about 20 to about 80% by weight based on the weight of said diclofenac.

40. The method of claim **34** wherein said means for enhancing said average T_{max} of said diclofenac comprises sodium bicarbonate.

41. The method of claim **34** wherein said means for enhancing said average T_{max} of said diclofenac comprises potassium bicarbonate.

42. The method of claim **34** wherein said diclofenac formulation is said powder formulation.

43. The method of claim **34** wherein said diclofenac formulation is said fast release layer.

* * * * *

EXHIBIT B

US007482377B2

(12) **United States Patent**
Reiner et al.

(10) **Patent No.: US 7,482,377 B2**
(45) **Date of Patent: *Jan. 27, 2009**

(54) **PHARMACEUTICAL COMPOSITIONS AND METHODS OF TREATMENT BASED ON DICLOFENAC**

(75) Inventors: **Alberto Reiner**, Como (IT); **Giorgio Reiner**, Como (IT)

(73) Assignee: **Kowa Pharmaceuticals America, Inc.**, Montgomery, AL (US)

(*) Notice: Subject to any disclaimer, the term of this patent is extended or adjusted under 35 U.S.C. 154(b) by 95 days.

This patent is subject to a terminal disclaimer.

(21) Appl. No.: **11/132,024**

(22) Filed: **May 18, 2005**

(65) **Prior Publication Data**

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Related U.S. Application Data

(63) Continuation of application No. 09/524,747, filed on Mar. 14, 2000, now Pat. No. 6,974,595, which is a continuation of application No. 09/192,493, filed on Nov. 17, 1998, now abandoned, which is a continuation of application No. PCT/EP97/02709, filed on May 15, 1997.

(30) **Foreign Application Priority Data**

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A61K 31/185 (2006.01)
A61K 31/19 (2006.01)

(52) **U.S. Cl.** **514/553**; 514/557; 514/576

(58) **Field of Classification Search** 514/553, 514/557, 576; 560/47
See application file for complete search history.

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Assistant Examiner—L. E. Crane
(74) *Attorney, Agent, or Firm*—Clark G. Sullivan

(57) **ABSTRACT**

New pharmaceutical compositions for oral use containing diclofenac together with alkali metal bicarbonates in amounts of from 20 to 80 by weight with respect to diclofenac are described. These compositions are entirely palatable and free from any unpleasant taste or other, side effects; in particular, these formulations permit to obtain in human patients higher C_{max} of the active principle and shorter T_{max} together with a lower coefficient of variation.

15 Claims, 10 Drawing Sheets

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FIG. 1

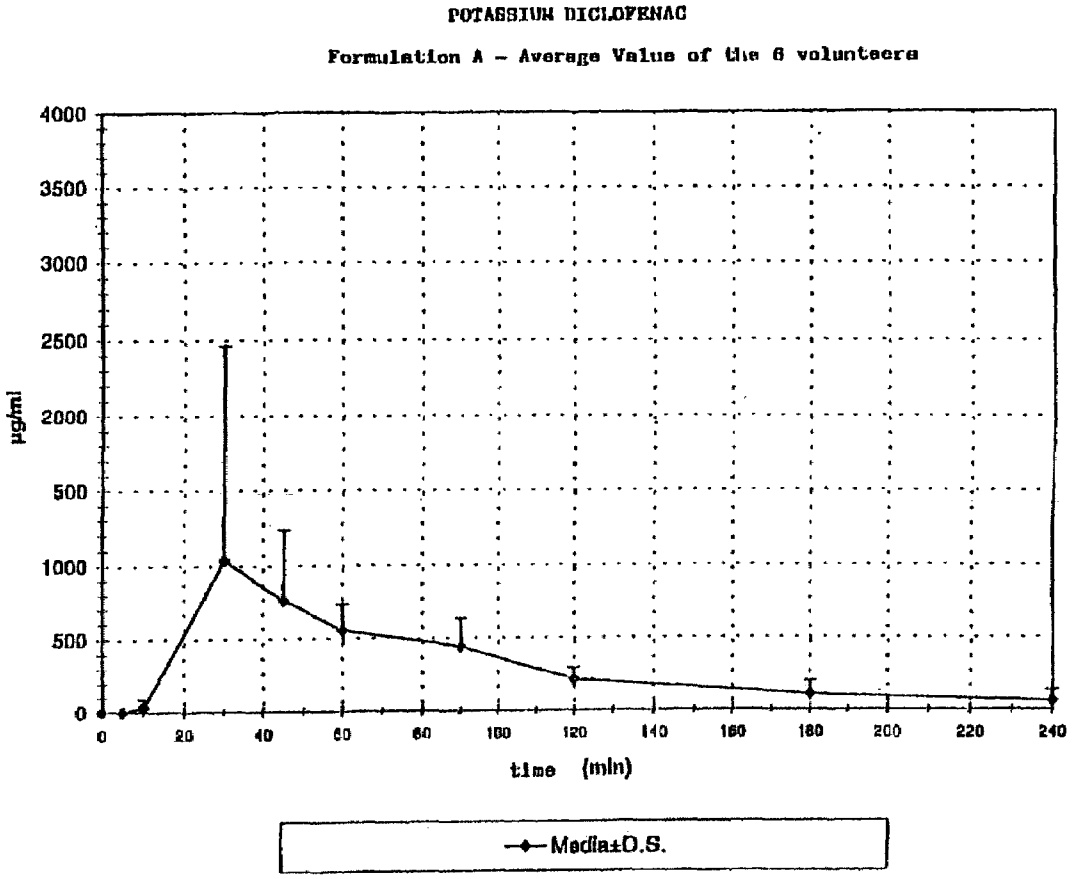

POTASSIUM DICLOFENAC
Formulation A – Average Value of the 6 volunteers
µg/ml
4000
3500
3000
2500
2000
500
1000
500
0
0
20
40
60
80
100
120
140
160
180
200
220
240
time (min)
Media±D.S.

FIG. 2

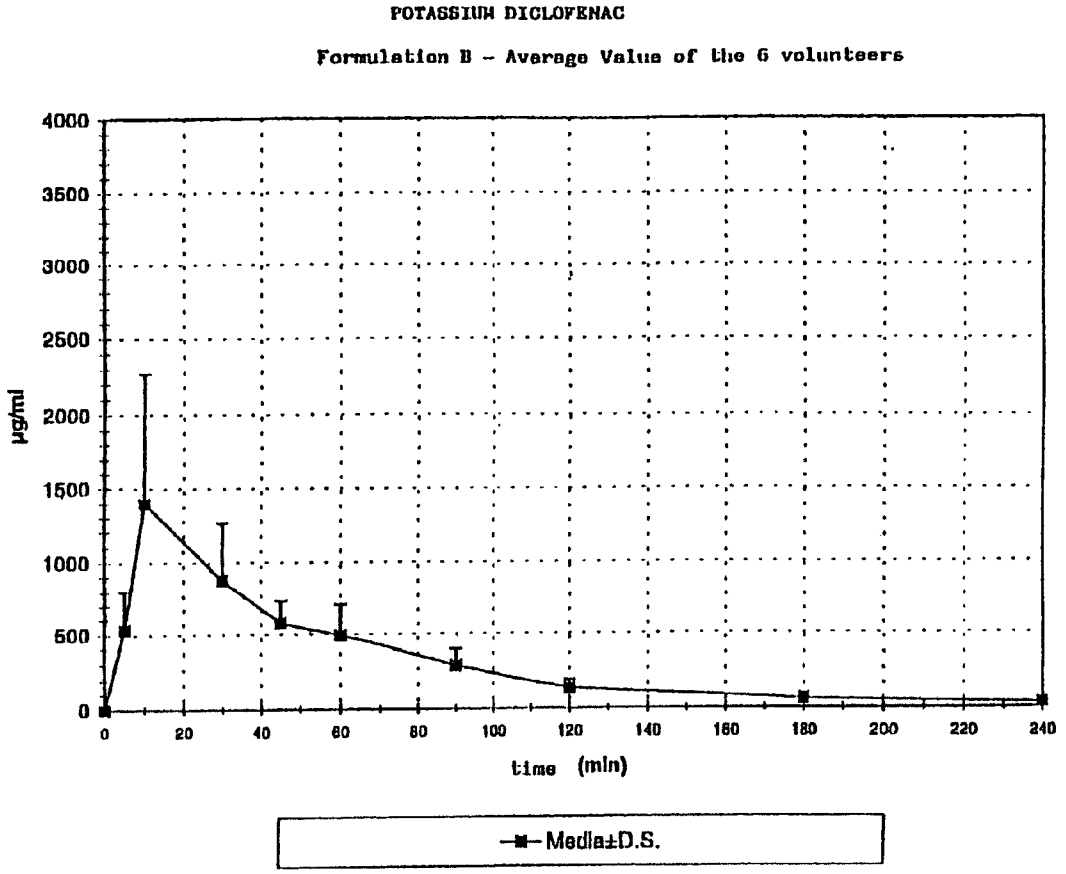

POTASSIUM DICLOFENAC
Formulation B - Average Value of the 6 volunteers
4000
3500
3000
2500
2000
1500
1000
500
0
µg/ml
0
20
40
60
80
100
120
140
160
180
200
220
240
time (min)
Media±D.S.

FIG. 3

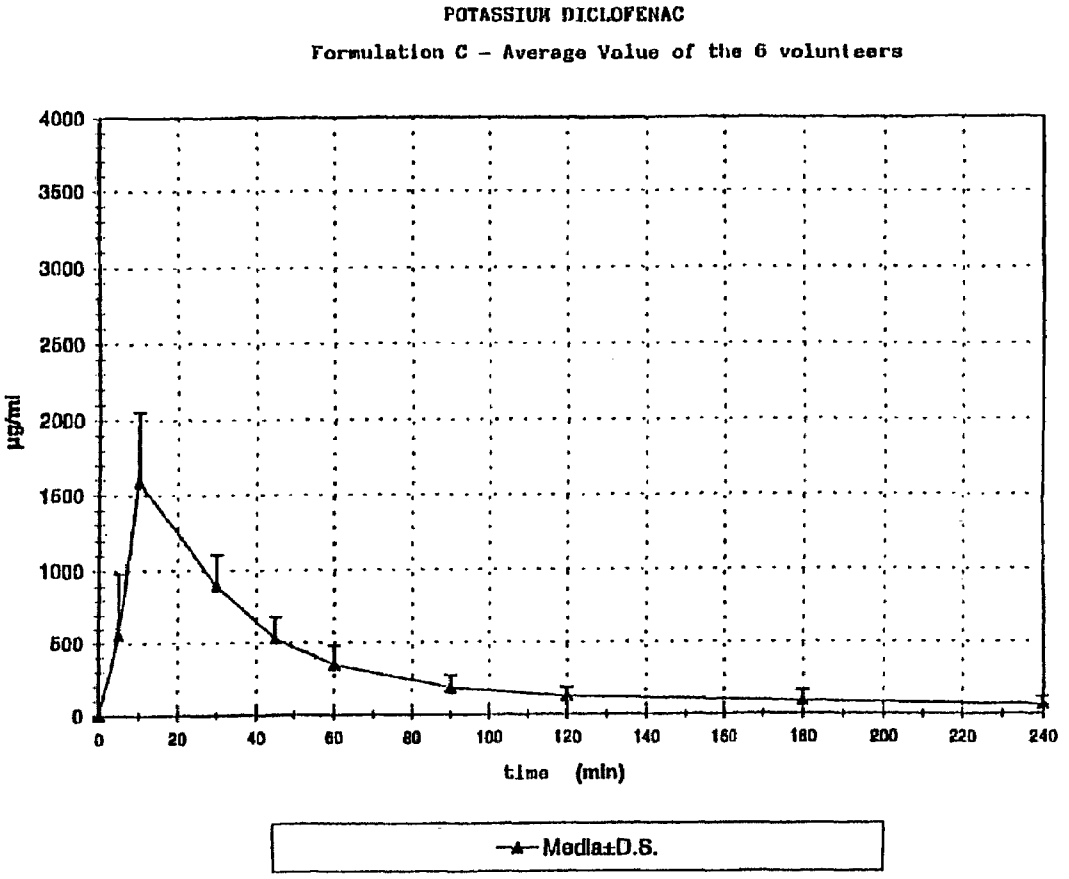

POTASSIUM DICLOFENAC
Formulation C – Average Value of the 6 volunteers
4000
3500
3000
2500
2000
1500
1000
500
0
µg/ml
0
20
40
60
80
100
120
140
160
180
200
220
240
time (min)
Media±D.S.

FIG. 4

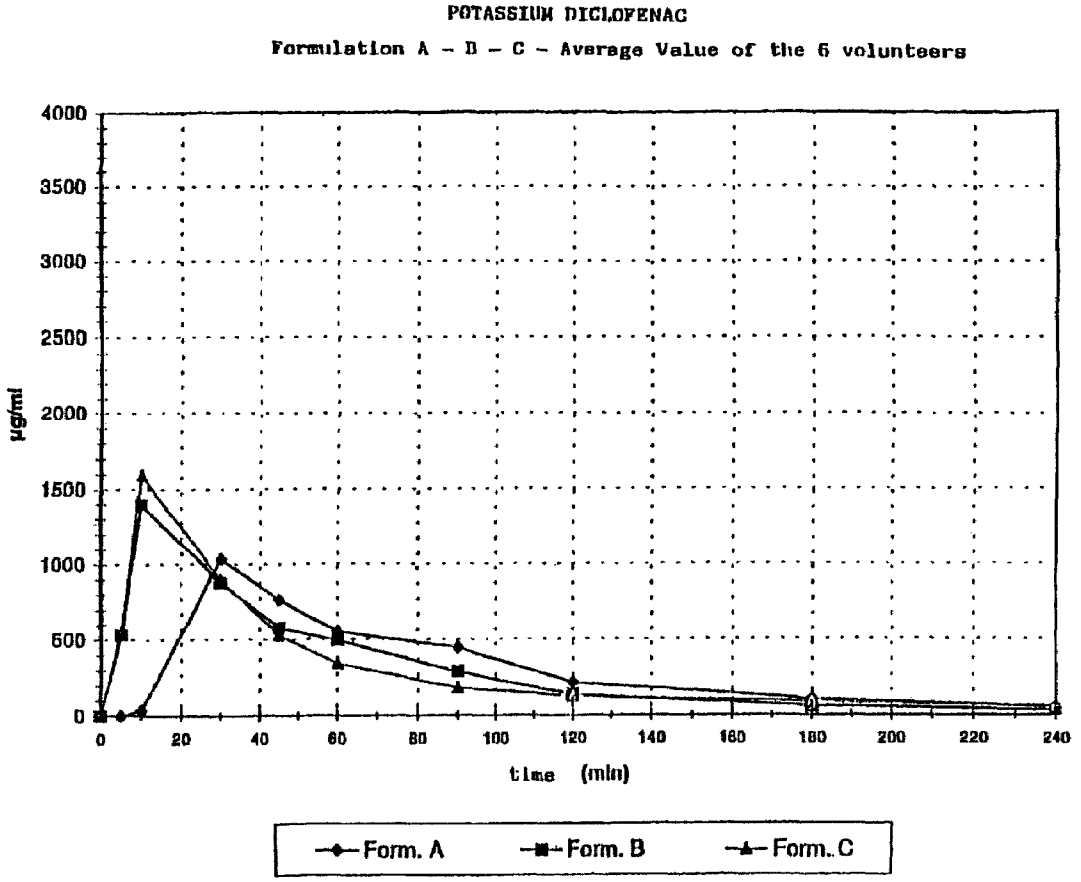

POTASSIUM DICLOFENAC
Formulation A – B – C – Average Value of the 6 volunteers
4000
3500
3000
2500
2000
1500
1000
500
0
µg/ml
0
20
40
60
80
100
120
140
160
180
200
220
240
time (min)
Form. A
Form. B
Form. C

FIG. 5

Mean, overlaid plasma concentration-time curves measured in all volunteers after administration of diclofenac test and reference formulations in linear and log-scale. Dose administered = 50 mg.

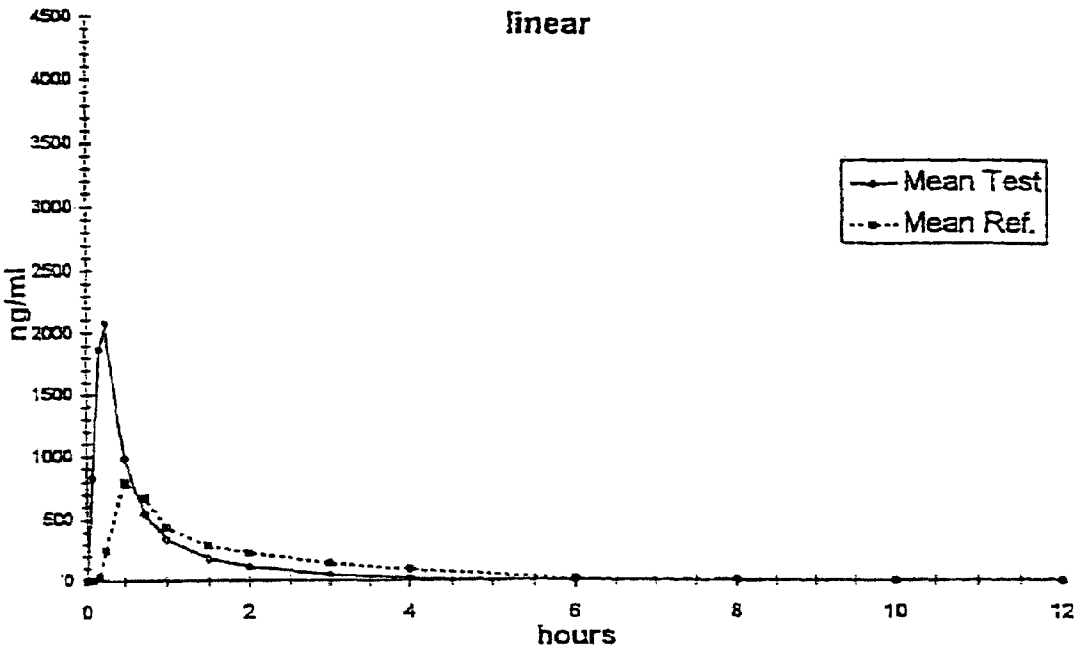


FIG. 6

Mean, overlaid plasma concentration-time profiles measured in all volunteers after administration of diclofenac T_1, T_2, R_1 (CATAFLAM®) and R_2 (VOLTAROL®) formulations; linear and log scales.

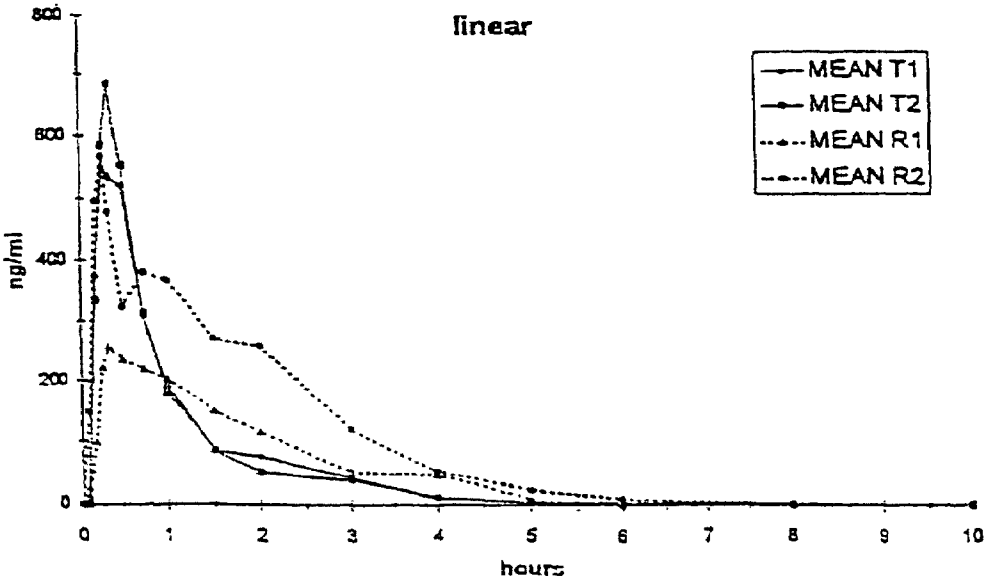


FIGURE 7

Mean plasma concentration-time profile of diclofenac measured in all volunteers after oral administration of T_1 formulation. Linear scale. Vertical bars are SD.

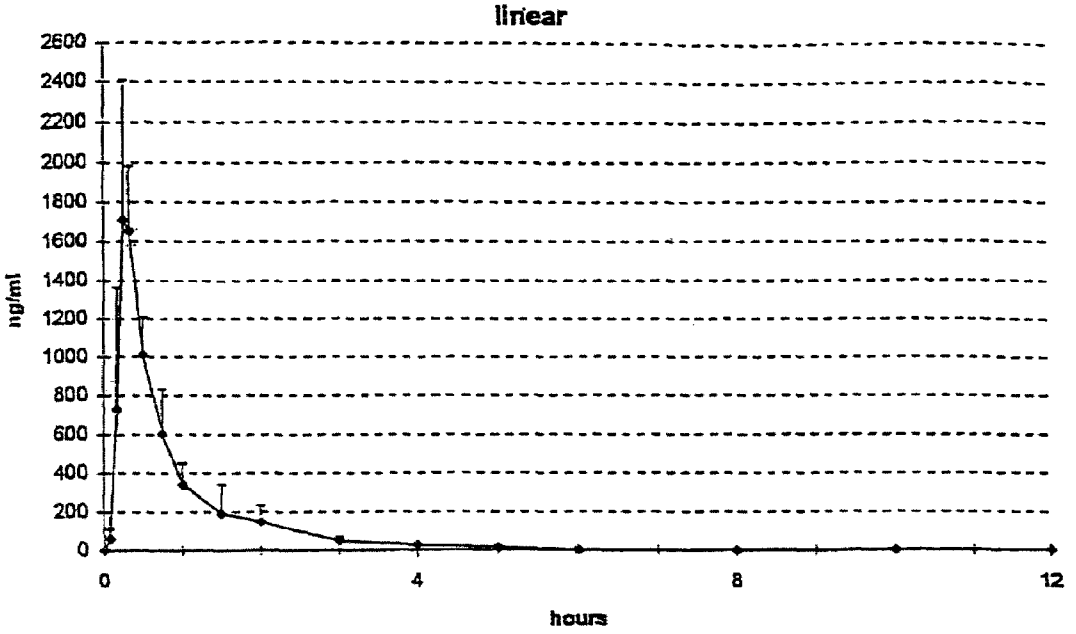


FIGURE 8

Mean plasma concentration-time profile of diclofenac measured in all volunteers after oral administration of T_2 formulation. Linear scale. Vertical bars are SD.

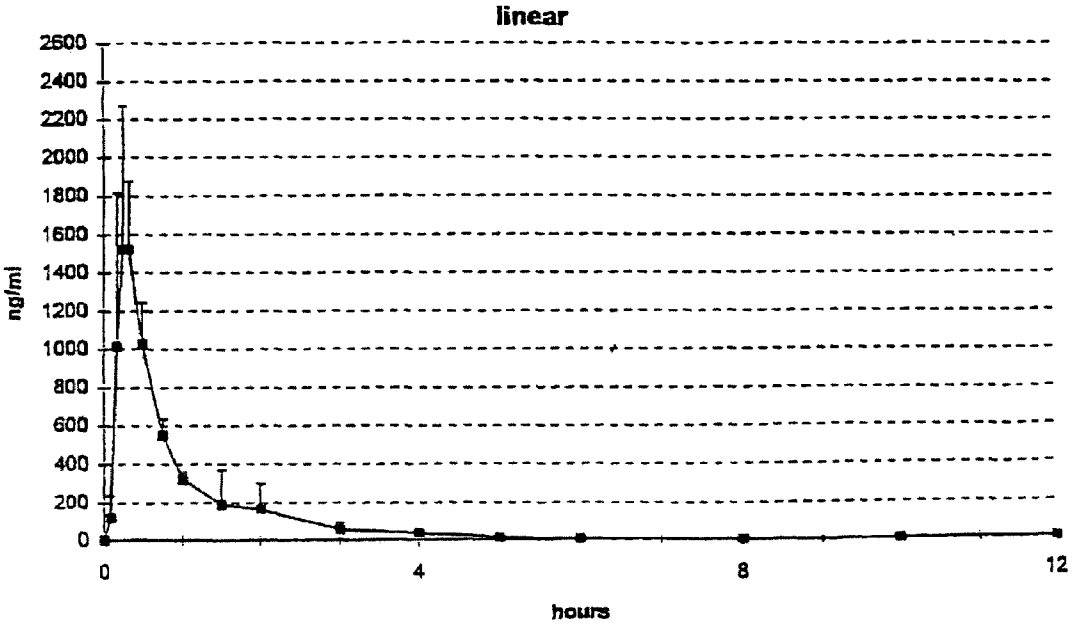


FIGURE 9

Mean plasma concentration-time profile of diclofenac measured in all volunteers after oral administration of R (VOLTARENE® RAPIDE) formulation. Linear scale. Vertical bars are SD.

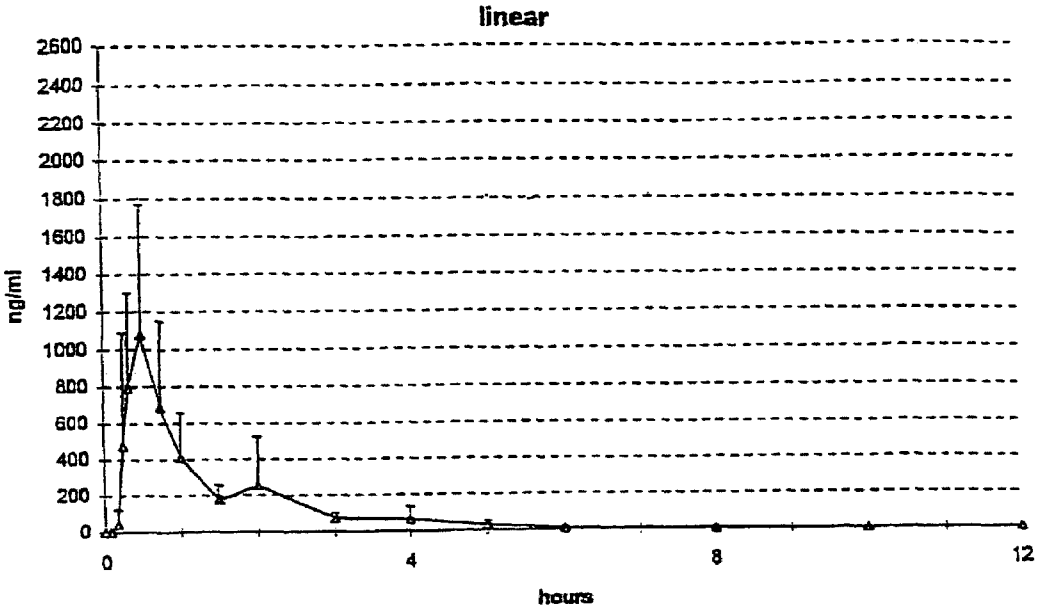
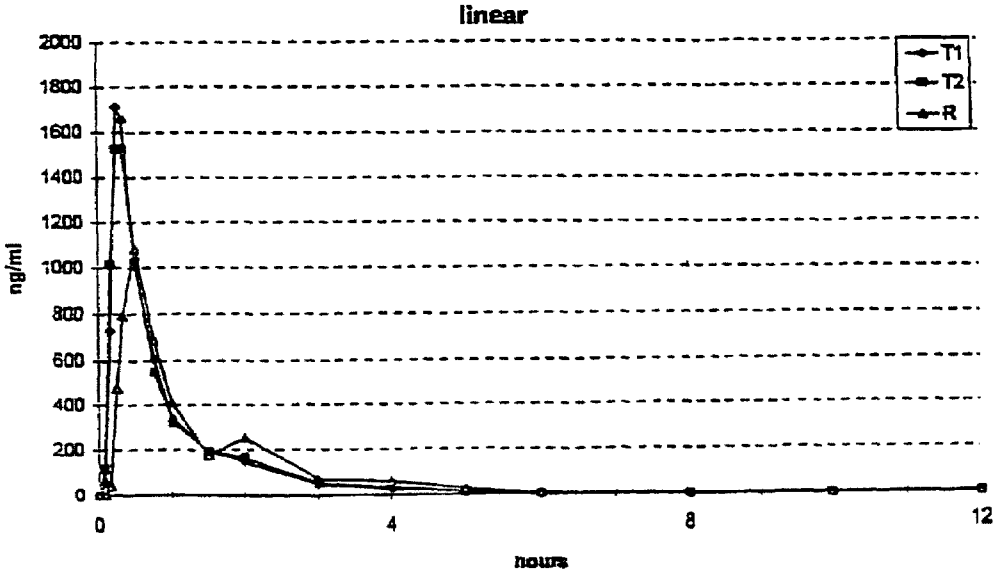


FIGURE 10

Mean, overlaid plasma concentration-time profile of diclofenac measured in all volunteers after oral administration of T_1, T_2 and R (VOLTARENE® RAPIDE) formulation. Linear and log scales.



PHARMACEUTICAL COMPOSITIONS AND METHODS OF TREATMENT BASED ON DICLOFENAC

RELATION TO PRIOR APPLICATIONS

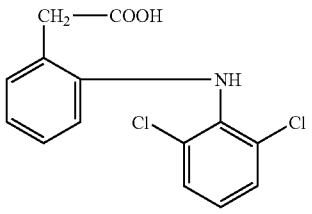
The present application is a continuation of U.S. Ser. No. 09/524,747, filed Mar. 14, 2000 now U.S. Pat. No. 6,974,595, which is a continuation in part of U.S. Ser. No. 09/192,493, filed Nov. 17, 1998, which is a continuation of PCT/EP97/02709 file May 15, 1997. The contents of the foregoing applications are incorporated herein by reference as if fully set forth herein.

FIELD OF INVENTION

The present invention relates to new immediate release pharmaceutical compositions containing [(2,6-dichloroanilino)-2-phenyl]-2-acetic acid (more commonly known as diclofenac) in acid and/or salt form, and therapeutic regimens involving same.

BACKGROUND OF INVENTION

Diclofenac is a non-steroidal drug which was invented at the end of the sixties by A. Sallmann and R. Pfister (NL-6,604,752 and U.S. Pat. No. 3,558,690 both to Ciba-Geigy) and whose structural formula is indicated below.



Diclofenac is widely dispensed and used owing to its well-known analgesic, anti-pyretic, anti-arthritic, anti-phlogistic and anti-rheumatic properties. It is generally taken orally in the form of normal tablets or tablets covered with coatings resistant to gastric juices, or rectally, or by injection, or topically.

The possibility of taking it in the form of sweets, tablets dissolving in the mouth, drages, chewing gum or other similar pharmaceutical forms or in formulations for the extemporary preparation of diclofenac-based aqueous solutions and/or suspensions would represent a different mode of administration which is definitely more suitable, especially for children and elderly persons.

Owing to its poor solubility in water, diclofenac is normally used in salt form; the salts of diclofenac customarily used are those of sodium, potassium or other alkali and alkaline earth metals, together with salts of organic nature, such as the salts of basic amino acids, such as lysine, arginine and ornithine, or other pharmacologically acceptable organic bases which have the ability to render the resulting salt soluble in water.

The pharmaceutical compositions of the diclofenac salts for oral use are generally 25 accompanied by side effects of not inconsiderable consequence: Diclofenac salts are in fact characterised by a particularly unpleasant and bitter taste and by the fact that they produce a sensation of strong astringency and cause an especially intense form of irritation in the buccal cavity, especially in the area of the larynx.

Although the first problem has been partly solved by using flavourings which are able in some manner to mask the taste, satisfactory solutions have still not been proposed for the two remaining problems.

Therefore, the pharmaceutical compositions containing diclofenac salts still have a poor palatability which limits their adoption and possible fields of application, despite the excellent therapeutic effect with which they are associated.

A second problem connected to diclofenac is that, when it is orally administered by means of immediate release formulations, the corresponding T_{max} (the time to the maximum plasma concentration) is usually located at about 1 hour since administration, this being of course a not completely satisfactory result when a prompt and strong analgesic/anti-pyretic effect is sought for. Furthermore, the corresponding coefficient of variation is normally in the range of 70-90%, which means that the T_{max} is strongly variable and dependent on the physical characteristics of the patient (Physicians' Desk Reference, 52 edition, 1998, pag. 1831). Attempts are therefore still being made in order to enhance the rate of absorption of diclofenac and to provide an earlier onset of the therapeutic effect (N. Davies, K. Anderson; Clinical Pharmacokinetics of Diclofenac, Clin. Pharmacokinet., 1997, September 33(3)).

The object of the present invention is therefore that of providing a fully palatable formulation of diclofenac which is able to generate a more rapid, uniform and foreseeable release of the active principle if compared to the compositions known in the art and presently available on the market. For the purposes of the present invention T_{max} means the time to the maximum plasma concentration whereas C_{max} is the maximum plasma concentration of the active principle, namely diclofenac.

DISCUSSION

It has now been found that, by adding alkali metal bicarbonates or mixtures thereof to the diclofenac in its acid and/or salt form, preferably in amounts of from 20 to 80% by weight based on the acid-form of diclofenac, pharmaceutical compositions can be obtained which are substantially free from the side effects mentioned above. The first object of the present invention is therefore represented by a pharmaceutical formulation for oral use containing diclofenac in acid and/or salt form together with alkali metal bicarbonates or mixtures thereof and customary excipients and adjuvants, wherein said alkali metal bicarbonates are preferably present in amounts of from 20 to 80% by weight based on the weight of diclofenac.

It has in fact been surprisingly demonstrated that the use of alkali metal bicarbonates in the above-mentioned ratio permits to achieve constant, reproducible and foreseeable blood levels of the active ingredient, with the consequent indisputable advantages from the therapeutic point of view; furthermore, it has also been found that the combined use of diclofenac together with alkali metal bicarbonates yields diclofenac-based pharmaceutical compositions in which the active ingredient is released more rapidly compared with normal formulations, bringing about higher blood levels and therefore a more immediate therapeutic effect; finally the so-obtained immediate release formulations are substantially palatable and free from aftertaste.

According to the preferred embodiment of the present invention, the amount of alkali metal bicarbonates to be added is comprised between 40 and 80% by weight, based on the weight of the acid-form diclofenac, whereas the alkali metal bicarbonates are selected from sodium and/or potassium

bicarbonates, diclofenac being normally present in the form of its sodium and/or potassium salts.

It has also been found, and forms a second subject of the present invention, that the addition of flavouring substances selected from mint, aniseed, ammonium glycyrrhizinate and mixtures thereof to the compositions containing the diclofenac salts and alkali metal bicarbonates produces a synergistic effect which completely eliminates all the above-mentioned palatability/astringency effects, providing pharmaceutical compositions which are entirely palatable (and/or drinkable in the case of those used for the preparation of solutions and/or suspensions) and free from aftertaste.

The flavouring substances may be used as such or supported on inert materials, for example maltodextrin, in order to obtain a better distribution of the granulates and to facilitate excellent dispersibility of the flavouring in solution. Preferably, they are absorbed on maltodextrin with a power of 1 to 2000 and 1 to 1000.

The amount of flavouring substances in its pure form is also preferably from ⅕ to 3 times the weight of the acid-form diclofenac.

These flavouring substances are used in the implementation of the present invention without altering their organoleptic properties and without depriving them of their intrinsic qualities of flavourings which are liposoluble and generally oily in the pure state.

As it will be clear from the examples, the immediate release formulations for oral use of the present invention containing from 10 to 60 mg of diclofenac in acid and/or salt form together with alkali metal bicarbonates or mixtures thereof in amounts of from 20 to 80% by weight based on the weight of diclofenac permit to generate in human patients an average C_{max} of diclofenac comprised between 400 and 2500 ng/ml independently on the age, sex or weight of the patients themselves.

Secondly, the formulations according to the present invention permit to obtain in humans an average T_{max} of Diolofenac after 5-30 minutes since administration, generally 13-27, independently on the amount of diclofenac contained therein and also independently on the age, sex, weight of the patient.

Furthermore, the T_{max} of the formulations of the present invention show a coefficient of variation which is about 44-86% lower than the presently marketed formulations; this is evidently an extremely important result from the clinical point of view as it is now possible to have a therapeutic effect of diclofenac which is foreseable, reproducible and independent of the sex, weight and health conditions of the patient.

Thus, the presently claimed diclofenac-based formulations permit to achieve a higher C_{max} in a shorter T_{max} and with a lower coefficient of variation if compared to the formulations available on the market, with therapeutic advantages which do not need to be commented.

According to the best mode for carrying out the present invention the pharmaceutical formulations will contain from 10 to 60 mg/dose of diclofenac in its potassium or sodium salt form together with 40 to 80% by weight of potassium or sodium bicarbonate based on the weight of diclofenac in its acid form, together with the usual excipients and adjuvants; even more preferably they will packaged as:

- a sachet or tablet formulation containing 50 mg of diclofenac potassium salt and 22 mg of potassium bicarbonate or 50 mg of diclofenac sodium salt and 19 mg of sodium bicarbonate;
- a sachet or tablet formulation containing 12.5 mg of diclofenac sodium salt 15 and 5.5 mg of potassium bicarbonate or 25 mg of diclofenac sodium salt and 11 mg potassium bicarbonate.

It will be by the way evident to any skilled in this art that the present formulations can also be used as immediate release layers of multilayered release pharmaceutical formulations containing diclofenac as one of the active ingredients; said formulations are therefore a further object of the present invention.

EXAMPLES

The following Examples are given purely by way of non-limiting illustration.

Example 1

Composition Dissolving Instantly in Water

	Active ingredients	
1)	Diclofenac potassium salt*:	50 mg
2)	Potassium bicarbonate:	22 mg
3)	Mint flavouring on maltodextrin (1:2000)**:	60 mg
4)	Aniseed flavouring on maltodextrin (1:1000)***:	104 mg
	Excipients and adjuvants	
5)	Saccharin:	4 mg
6)	Aspartame:	10 mg
7)	Mannitol:	50 mg
8}	Saccbarose*** *q.s.:	2 g

*If it is desired to prepare compositions based on diclofenac sodium salt, it is advantageous to use sodium bicarbonate in a quantity of approximately 38% by weight based on the weight of the diclofenac sodium salt present. Sodium carbonate may also be added to the sodium bicarbonate, maintaining the following optimum proportions: 27% of sodium bicarbonate and 4-5% of sodium carbonate, always based on the amount by weight of diclofenac sodium salt present.

**The title of the pure mint essence, as obtained according to the Dean-Stark method, is of 18% by weight; the related amount is therefore in this case of 10.8 mg.

***The title of the pure anise essence, as obtained according to the Dean-Stark method, is of 14.5% by weight, the related amount is therefore in this case of 16 mg.

****The presence of saccharose is not strictly necessary; in its absence, a composition having a very limited granulate content is obtained which is perfectly 20 soluble in contact with water. In that case, nothing is changed from the point of view of tolerability in contact with the mucosa and from the point of view of the palatability of the drinkable solution.

Preparation

Components 1, 2, 5, 6 and 7 are mixed in a suitable mixer, and the mixture so obtained is wetted with 95% ethanol. Granulation is carried out with a 66 mm mesh and the granulate is preferably dried in current of air.

Components 3, 4 and 8, which have already been granulated using a mesh of the same granulometry, are then added and the whole is mixed.

The mixture is then introduced into a metering machine for filling packets or similar containers.

Example 2

Tablet for Dissolving in the Mouth

	Active ingredients	
1)	Diclofenac potassium salt*:	50 mg
2)	Potassium bicarbonate:	35 mg
3)	Mint flavouring on maltodextrin** (1:2000) + gum arabic (E 414):	50 mg

-continued

4) Aniseed flavouring (1:1000) on maltodextrin*** + silicon dioxide (E 551):	120 mg
Excipients and adjuvants	
5) Saccharin:	50 mg
6) Aspartame:	12 mg
7) Mannitol:	20 mg
8) Saccharose****:	300 mg

* to *** see Example 1

Example 3

Gum Tablet

Active ingredients	
1) Diclofenac potassium salt*:	50 mg
2) Potassium bicarbonate:	35 mg
3) Mint flavouring on maltodextrin**:	30 mg
4) Aniseed flavouring on maltodextrin***:	80 mg
Excipients and adjuvants	
5) Mannitol:	30 mg
6) Menthol:	0.01 mg
7) Gum base:	600 mg
8) Sorbitol:	700 mg
9) Saccharin:	3 mg
10) Hydroxypropylmethycellulose:	33 mg
11) Colouring agent:	7 mg

* to *** see Example 1

Example 4

Comparative Test

The packaged composition containing 50 mg of diclofenac potassium of Example 1 (formulation C) was subjected to a pharmacokinetic test for comparison with a similar composition not containing alkali metal carbonates and bicarbonates (formulation B), and with a second composition in tablet form (formulation A) produced by Ciba-Geigy (Voltaren Rapid®), also in this case not containing alkali metal carbonates and bicarbonates, both formulations A and B containing 50 mg of diclofenac potassium.

This comparative evaluation was carried out on the same 6 healthy volunteers in accordance with the experimental plan described hereinafter.

Experimental scheme: Single-dose study using three methods in randomised 15 cross-over with a wash-out of three days.

Sampling times: Oh (before administration), 5 min, 10 min, 30 min, 45 min, 1 h, 1.5 h, 2 h, 3 h, 4 h, 6 h, 8 h, after each administration.

Blood sample treatment: 8MI in heparinised test tubes, centrifugation for 15 min at 1500 rev/min, subdivided into two fractions and subsequently frozen at −200 C.

Times: wash-out of two days between treatments.

Determination method: HPLC, with internal standard, sensitivity 10 ng/ml

Analysis Method

Column: Nova Pak C18, 3.9×150 mm, 4 um Waters S.p.A.—Vimodrone, Italy.

Eluant: NaH2PO4 0.01 M+0.1% TEA, pH 3.0 (H3PO4)/acetonitrile, 60/40.

Flow: 1.2 ml/min

Detection: UV/275 nm

Temperature: 30° C.

Injection: 50 al

Analysis time: 16 min.

Sample Preparation

10 al of the internal standard methanolic solution, and flufenamic acid (corresponding to 1320 ng) are added to 1 ml of defrosted plasma in 10 ml glass test tubes. The tubes are agitated in a Vortex mixer for 1 minute. 0.5 ml of a 0.5N HCl/1N NaCl solution is added. The whole is agitated in a Vortex mixer for 1 minute. 6 ml of a 95/5 n-hexane/isopropanol solution are added.

The mixture is then agitated in the Vortex mixer for a further 15 minutes. Centrifugation is carried out at 3000 rev/min for 15 minutes and the organic phase is transferred to fresh 10 ml glass test tubes and evaporated to dryness in a centrifugal evaporator under vacuum at ambient temperature. The whole is taken up in 200 al of a 70/30 acetonitrile/water solution, and the precipitate is dissolved under ultrasound for 2 minutes.

FIGS. **1**, **2** and **3** show the concentrations of diclofenac in the blood of the six volunteers as regards formulations A, B (Ciba-Geigy comparative formulations) and C (formulation corresponding to the composition of Example 1), respectively.

As will be appreciated, the blood concentration of the formulation of the present invention has, compared with the comparative formulations, a more constant and uniform pattern. This characteristic is also found in FIGS. **4**, **5** and **6** which show the average values corresponding to the blood levels of the six volunteers together with the corresponding standard deviation.

The result is clear and surprising: compared with the sample compositions, the compositions of the present invention permit constant, reproducible and foreseeable blood levels of the active ingredient, irrespective of the characteristics of the volunteer (weight, age, etc), with the consequent indisputable advantages from the therapeutic point of view.

Finally, FIG. **7** shows, by comparison, the graphs relating to the average values of the six volunteers (that is to say, the preceding FIGS. **4**, **5** and **6**); as will be noted, the formulation of the present invention permits, in addition to the advantages already mentioned, the attainment of a blood peak higher than that of the other formulations.

Example 5

Two Layered Tablet (Fast and Slow Release)

Fast release layer	
1) Diclofenac potassium salt:	15 mg
2) Potassium bicarbonate:	30 mg
3) Lactose:	13.2 mg
4) Maize starch (intragranular):	6 mg
5) Methyl cellulose:	0.12 mg
6) Sodium laurylsulfate:	0.06 mg
7) Maize starch (extragranular):	9 mg
8) Crospovidone:	0.6 mg
9) Sodium carboxymethylstarch:	1.5 mg

-continued

10) Magnesium stearate:	2.7 mg
11) Colloidal silicon dioxide:	0.6 mg
Slow release layer	
1) Diclofenac potassium salt:	70 mg
2) Potassium bicarbonate:	30.8 mg
3) Lactose:	32.2 mg
4) Polyvinylpyrrolidone:	1.16 mg
5) Hydroxypropylmethylcellulose:	70 mg
6) Magnesium stearate:	0.84 mg
7) Colloidal silicon dioxide:	0.21 mg
8) Talc:	3.92 mg
9) Polyethylene glycol:	0.56 mg

Example 6

Drops

1) Diclofenac potassium salt:	75 g
2) Methyl p-oxybenzoate:	2.7 g
3) Propyl p-oxybenzoate:	0.3 g
4) Aspartame:	37.5 g
5) Potassium bicarbonate:	37.5 g
6) Glycerol:	300 g
7) Ethyl alcohol:	450 g
8) Water q.s.:	1500 g
Possible modifications:	
a) Addition of sodium metabisulfite (0.06%)	
b) Addition of sodium metabisulfite (0.06%) Mint flavouring (1.25%) Strawberry flavouring (0.75%)	

Example 7

Drops

1) Diclofenac potassium salt:	37.5 g
2) Methyl p-oxybenzoate:	2.7 g
3) Propyl p-oxybenzoate:	0.3 g
4) Aspartame:	37.5 g
5) Potassium bicarbonate:	18.75 g
6) Saccharin:	6.0 g
7) Glycerol:	300 g
8) Ethyl alcohol:	450 g
9) Water q.s.:	1500 g
Possible modifications:	
a) Addition of sodium metabisulfite (0.03%)	
b) Addition of sodium metabisulfite (0.03%) Mint flavouring (1.25%) Strawberry flavouring (0.75%)	

Example 8

Mouthwash

1) Diclofenac potassium salt:	0.75 g
2) Glycerol:	50 g

-continued

3) Sorbitol:	12 g
4) Saccharin:	0.5 g
5) Aspartame:	1.0 g
6) Methyl p-oxybenzoate:	0.5 g
7) Propyl p-oxybenzoate:	0.1 g
8) Mint flavouring:	1.0 g
9) Ethyl alcohol:	100 g
10) Potassium bicarbonate:	0.33 g
11) Water q.s.:	500 ml

Example 9

Gum-Paste

1) Diclofenac potassium salt:	5.0 g
2) Glycerol:	630 g
3) Sodium benzoate:	5.0 g
4) Silica (Wessalon S ® - Degussa):	120 g
5) Silica (Siddent 9 ® - Degussa):	80 g
6) Cellulose gum:	3.0 g
7) Polyethyleneglycol 600:	30 g
8) Sodium lauroyl sarcosinate (or sodium lauryl sulfate):	60 g
9) Mint flavouring:	10 g
10) Sodium saccharin:	1.0 g
11) Aspartame:	3.0 g
12) Potassium bicarbonate:	2.2 g
13) Water q.s.:	1 kg

Example 10

Tooth-Paste

1) Diclofenac potassium salt:	5.0 g
2) Glycerol:	630 g
3) Sodium benzoate:	5.0 g
4) Silica (Wessalon S ® - Degussa):	20 g
5) Silica (Siddent 9 ® - Degussa):	80 g
6) Cellulose gum:	3.0 g
7) Polyethylenglycol 600:	30 g
8) Sodium lauroyl sarcosinate (or sodium lauryl sulfate):	60 g
9) Mint flavouring:	10 g
10) Sodium saccharin:	1.0 g
11) Aspartame:	3.0 g
12) NaF:	1.0 g
13) Na_2FPO_3	4.0 g
14) Potassium bicarbonate:	2.2 g
15) Water q.s.:	1 kg

Example 11

Tablet

1) Diclofenac potassium salt:	50 mg
2) Mannitol:	50 mg
3) Potassium bicarbonate:	22 mg
4) Maize starch (intragranular):	10 mg
5) Methyl cellulose:	0.2 mg

-continued

6) Sodium laurylsulfate:	0.1 mg
7) Maize starch (extragranular):	15 mg
8) Crospovidone:	1.0 mg
9) Sodium carboxymethylstarch:	2.5 mg
10) Magnesium stearate:	4.5 mg
11) Colloidal silicon dioxide:	10 mg

Example 12

Comparative Test

In the present experiment a sachet formulation containing 50 mg of diclofenac potassium was compared to a bioequivalent sugar coated fast release tablet also containing 50 mg of diclofenac potassium, produced and marketed in Italy by Novartis as Cataflarn®.

The sachet formulation according to the present invention had the following composition:

1) Diclofenac potassium salt:	50 mg
2) Potassium bicarbonate:	22 mg
3) Mint flavour:	50 mg
4) Anice flavour	100 mg
5) Saccharin sodium:	4 mg
6) Aspartame:	10 mg
7) Mannitol:	50 mg
8) Sucrose sugar crystals:	1714 g

The above test formulation and the Cataflam® formulation were administered as a single dose to 24 healthy volunteers of both sexes. The pharmacokinetic parameters obtained with the two different formulations are reported in table 1 and in FIG. **5**. As it will be easily appreciated, the rate of absorption was considerably faster with the sachet formulation of the present invention than with Catafiam®, the sachet formulation having a higher average C_{max} (2213 vs 1071 ng/ml) and a shorter average T_{max} (0.228 vs 0.885 hours); furthermore, the T_{max} of the sachet formulation shows a coefficient of variation lower than the reference formulation (16% vs 97%), this being an extremely important result from the clinical point of view regarding the healing of the pain in terms of quick time and repeteability inter-subjects in order to reach the C_{max}.

Example 13

Comparative Test

Following to the excellent results obtained in example 12, two tablet formulations containing 12.5 or 25 mg. of diclofenac sodium salt and potassium bicarbonate (in the same weight ratio) have been prepared.

The tablet formulations had the following composition (in mg):

	Cores	
Diclofenac sodium	12.5	25
Mannitol	25	50
Lactose monohydrate	23.75	47.5
Potassium bicarbonate	5.5	11
Maize starch	22.5	45
Methylcellulose	0.075	0.15
Sodium laurylsulphate	0.125	0.25
Crospovidone	3	6
Ultramyl	5	10
Coloidal silica	0.55	1.1
Cellulose microcrystalline	0.5	1
Magnesium stearate	1.5	3
Purified water q.s.	100	200
Coating		
Opadry OY-3 5009 red	2	4
Macrogol 400	0.25	0.5

A four-way comparative bioavailability study was carried out on 18 healthy volunteers of both sexes in order to evaluate the in vivo results of the pharmacokinetic profiles of the present formulations if compared to those of bioequivalent fast release formulations such as Cataflam® (25 mg of diclofenac potassium) and Voltarol® (50 mg of diclofenac sodium), both by Novartis. The results, which are summarized in FIG. **6**, indicate that T_{max} is prompter with the present formulations (T1=26 min, T2=24.6 min vs R1=71.4 min and R2=40.8 min) and that C_{max} is higher (T1=847 ng/ml and T2=861 ng/ml vs R1=452 ng/ml and R2=703 ng/ml); furthermore, the T_{max} of both present formulations shows a coefficient of variation lower than reference formulations (T1=46% and T2=49% vs R1=87% and R2=96%).

Example 14

Comparative Test

A further comparative test was carried out on immediate release formulations according to the present invention, containing 50 mg of diclofenac potassium and 22 mg of potassium bicarbonate, manufactured with different that is, respectively: T1=wet granulation using alcohol, T2=dry granulation by direct compression. The composition in mg of the two formulations is herebelow reported:

Diclofenac potassium	50	50
Potassium bicarbonate	22	22
Mannitol/pearlitol 400 DC	119.9	
Mannitol EP cf		50
Maize starch		25
Methocel A4C		0.2
Sodium laurylsulphate	0.1	0.1
Polyplasdone XL	6	1
Ultramyl		2.5
Magnesium stearate	2	4.5
Silicium aerosil		1
Core mass	200	156.3

A comparative bioavailabilty study was carried out on 6 healthy volunteers of both sexes in order to evaluate the in vivo results of the pharmaokinetic profiles of the present formulations if compared to those of a bioequivalent fast release formulation such as Voltaren Rapid® (50 mg of diclofenac potassium), both by Novartis. The results, which are reported in FIGS. **7-10** are also in this case excellent: the T_{max} is in fact prompter with the present formulations (T1=18.6 min, T2=16.8 min vs R1 40.8 min) and the C_{max} is higher (T1=1878.3 ng/ml and T2=1744.8 ng/ml vs R1 1307 ng/ml); furthermore, also in this case the T_{max} of both present formulations shows a coefficient of variation lower than reference formulation (T1=12.9% and T2=25% vs R1=95.6%).

TABLE 1

Pharmacokinetic parameters for two different diclofena formulations: test (Diclofenac potassium salt sachets) and reference (Diclofenac potassium salt sugar coated tablets)

	t_{max} (h)		C_{max} (ng/mL)		$t_{1/2}$ (h)		AUC_{0-1} (ng · mL^{-1} – h)	
Vol. no.	Test	Ref.	Test	Ref.	Test	Ref.	Test	Ref.
Vol. 1	0.250	0.500	1573.000	1186.211	1.505	0.939	1024.511	885.549
Vol. 2	0.250	4.000	2382.368	965.100	0.875	1.358	1653.124	2092.036
Vol. 3	0.184	1.000	2614.655	1352.400	0.796	1.610	1687.529	1763.484
Vol. 4	0.250	3.000	2404.848	735.454	0.996	1.132	1881.944	1834.958
Vol. 5	0.250	0.500	2971.457	1405.000	1.667	1.903	1819.756	1687.075
Vol. 6	0.250	0.750	2158.700	1351.500	0.843	0.650	1197.716	1091.996
Vol. 7	0.250	0.750	1739.200	1741.717	0.596	0.658	1448.713	1301.887
Vol. 8	0.250	0.500	1715.350	534.300	0.818	1.111	991.864	1126.414
Vol. 9	0.250	0.750	444.112	747.800	0.787	1.188	669.084	886.300
Vol. 10	0.267	0.750	2350.100	1110.400	0.960	1.070	1327.808	1020.286
Vol. 11	0.167	0.500	1867.200	1465.502	1.141	0.762	1337.821	892.870
Vol. 12	0.167	0.500	4273.026	1432.200	1.052	0.697	1703.655	1139.003
Vol. 13	0.250	0.500	2097.089	1155.371	1.313	1.198	1486.526	1233.531
Vol. 14	0.167	0.250	2242.684	967.795	0.997	0.837	987.522	927.726
Vol. 15	0.184	0.500	2040.247	1129.957	0.724	0.804	1213.725	1040.424
Vol. 16	0.250	0.750	2143.692	818.200	0.560	1.199	1186.603	1250.221
Vol. 17	0.250	1.500	1527.845	480.900	2.752	1.309	958.821	978.797
Vol. 18	0.250	1.000	1859.608	666.500	1.630	1.383	1131.413	933.008
Vol. 19	0.250	0.750	1537.508	770.100	1.726	1.137	980.348	906.275
Vol. 20	0.250	0.250	1956.004	655.100	0.853	0.883	1309.289	1036.836
Vol. 21	0.250	0.500	3551.360	2421.060	1.322	1.233	2147.217	1639.619
Vol. 22	0.167	0.500	2464.978	1274.648	0.611	0.624	1038.817	816.924
Vol. 23	0.167	0.750	2304.351	453.500	2.066	0.862	1161.414	1049.327
Vol. 24	0.250	0.500	2901.504	894.337	0.970	1.279	1645.384	1086.512
Mean	0.228	0.885	2213.370	1071.461	1.148	1.076	1332.942	1192.544
SD	0.038	0.860	743.099	450.780	0.523	0.320	358.048	350.116
CV %	16.300	97.091	33.573	42.072	45.557	29.700	26.862	29.359
Min.	0.167	0.250	444.112	453.500	0.560	0.624	669.084	816.924
Max.	0.267	4.000	4273.026	2421.060	2.752	1.903	2147.217	2092.036
Geom. Mean	0.225	0.692	2070.719	987.180	1.056	1.032	1287.195	1150.713
Median	0.250	0.625	2151.196	1039.098	0.983	1.122	1261.507	1067.920

	AUC_{0-0} (ng · mL^{-1} – h)		C_1		C_{max}/AUC_{U-o} (h^1)		AUC extrapolated (%)	
Vol. no.	Test	Ref.	Test	Ref.	Test	Ref.	Test	Ref.
Vol. 1	1050.137	910.868	11.800	18.700	1.498	1.302	2.37	0.00
Vol. 2	1693.172	2092.036	31.700	13.500	1.407	0.461	1.82	1.38
Vol. 3	1718.755	1788.111	27.200	10.600	1.521	0.756	0.83	1.15
Vol. 4	1897.754	1856.346	11.000	13.100	1.267	0.396	1.39	1.88
Vol. 5	1845.486	1719.478	10.700	11.800	1.610	0.817	1.56	1.90
Vol. 6	1216.693	1113.146	15.600	22.500	1.774	1.214	2.50	1.79
Vol. 7	1485.867	1325.661	43.200	25.500	1.170	1.314	1.46	1.78
Vol. 8	1006.522	1146.775	12.400	12.700	1.704	0.466	3.08	2.75
Vol. 9	690.354	911.329	18.700	14.600	0.643	0.821	1.74	1.80
Vol. 10	1351.357	1038.971	17.000	12.100	1.739	1.069	3.01	3.01
Vol. 11	1379.311	920.579	25.200	25.200	1.354	1.592	1.62	2.03
Vol. 12	1731.709	1162.638	18.500	23.500	2.468	1.232	1.26	1.56
Vol. 13	1505.454	1253.088	10.000	11.300	1.393	0.922	2.58	2.26
Vol. 14	1013.665	949.163	18.200	17.700	2.212	1.020	1.91	2.86
Vol. 15	1237.399	1071.029	22.700	126.400	1.649	1.055	1.33	1.58
Vol. 16	1202.653	1270.280	19.900	11.600	1.782	0.644	4.16	2.80
Vol. 17	1000.433	1006.986	10.500	14.900	1.527	0.478	5.51	2.26
Vol. 18	1197.411	954.597	28.100	10.800	1.553	0.698	2.57	2.11
Vol. 19	1006.229	925.835	10.400	11.900	1.528	0.832	2.03	2.02
Vol. 20	1336.472	1058.242	22.400	16.800	1.464	0.619	1.19	1.07
Vol. 21	2173.030	1657.372	13.500	10.000	1.634	1.461	1.75	1.68
Vol. 22	1057.293	830.908	21.000	15.500	2.331	1.534	3.13	1.80
Vol. 23	1198.950	1068.588	12.600	15.500	1.922	0.424	2.19	1.94
Vol. 24	1682.290	1108.024	26.400	11.700	1.725	0.807	2.10	1.78
Mean	1361.600	1214.169	19.113	15.725	1.620	0.914	2.213	1.883
SD	358.359	348.108	8.244	5.160	0.377	0.365	1.035	0.641
CV %	26.319	28.671	43.134	32.812	23.277	39.991	46.795	34.056
Min.	690.354	830.908	10.000	10.000	0.643	0.396	0.833	0.000
Max.	2173.030	2092.036	43.200	26.400	2.468	1.592	5.512	3.010
Geom. Mean	1316.580	1173.325	17.609	15.011	1.573	0.841	2.023	//
Median	1286.936	1089.527	18.350	14.050	1.582	0.827	1.974	1.843

The invention claimed is:

1. A method of treating pain comprising administering to a host in need thereof a pharmaceutical formulation for oral administration containing diclofenac in its acid and/or salt form together with one or more alkali metal bicarbonates and customary excipients and adjuvants, wherein said alkali metal bicarbonates are present in an amount of from 20 to 80% by weight based on the weight of the acid form of diclofenac, and further wherein said formulation when administered is an intact tablet, or a powder formulation dissolved or dispersed in water, and wherein said formulation contains not more than 50 mg of diclofenac potassium or the equivalent amount of diclofenac or an alternative pharmaceutically acceptable diclofenac salt.

2. The method of claim 1 wherein said diclofenac is present in its potassium and/or sodium salt form.

3. The method of claim 2 wherein said formulation is administered as an intact tablet.

4. The method of claim 2 wherein said formulation is administered as a powder formulation dissolved or dispersed in water.

5. The method of claim 2 wherein said alkali metal bicarbonates are potassium and/or sodium bicarbonates.

6. The method of claim 1 wherein said formulation is administered as an intact tablet.

7. The method of claim 1 wherein said formulation is administered as a powder formulation dissolved or dispersed in water.

8. The method of claim 1 further comprising, before administering said formulation, providing a unit dose powder of diclofenac in acid and/or salt form and dissolving or dispersing said diclofenac in water to provide said formulation.

9. The method of claim 1 wherein said formulation is a liquid.

10. The method of claim 1 wherein said formulation comprises diclofenac potassium and potassium bicarbonate.

11. A method of treating pain comprising administering to a host in need thereof a pharmaceutical formulation for oral administration containing diclofenac as 50 mg. of diclofenac potassium together with one or more alkali metal bicarbonates or carbonates or mixtures thereof and customary excipients and adjuvants, wherein said alkali metal bicarbonates or carbonates or mixtures thereof are present in an amount of from 20 to 80% by weight based on the weight of the acid form of diclofenac, and further wherein said formulation when administered is an intact tablet or a powder formulation dissolved or dispersed in water.

12. The method of claim 11 wherein said formulation is a tablet comprising 50 mg. of diclofenac potassium.

13. The method of claim 11 further comprising, before administering said formulation, providing a unit dose powder of diclofenac potassium and dissolving or dispersing said diclofenac potassium in water to provide said formulation.

14. The method of claim 11 wherein said formulation is a liquid.

15. A method of treating pain according to claim 1, comprising orally administering to a host in need thereof a pharmaceutical formulation for oral administration containing diclofenac in sodium or potassium salt form together with sodium or potassium bicarbonates or mixtures thereof and customary excipients and adjuvants, wherein said sodium or potassium bicarbonates are present in an amount of from 20 to 80% by weight based on the weight of the acid form of diclofenac.

* * * * *

EXHIBIT C

US007759394B2

(12) **United States Patent**
Reiner et al.

(10) **Patent No.: US 7,759,394 B2**
(45) **Date of Patent: Jul. 20, 2010**

(54) **DICLOFENAC FORMULATIONS AND METHODS OF USE**

(75) Inventors: **Giorgio Reiner**, Como (IT); **Alberto Reiner**, Como (IT); **Andreas Meyer**, Neuenburg (DE)

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(21) Appl. No.: **11/455,120**

(22) Filed: **Jun. 16, 2006**

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A61K 31/185 (2006.01)
C07C 229/00 (2006.01)

(52) **U.S. Cl.** **514/553**; 514/557; 514/576; 560/47

(58) **Field of Classification Search** 514/553, 514/557, 576; 560/47
See application file for complete search history.

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(57) **ABSTRACT**

Methods and formulations are provided for treating migraine and other acute pain episodes using diclofenac, and formulations of diclofenac that provide both rapid and sustained relief from acute pain. Methods and formulations are also provided for treating symptoms that often accompany migraine and acute pain such as photophobia, phonophobia, nausea and vomiting.

25 Claims, 1 Drawing Sheet

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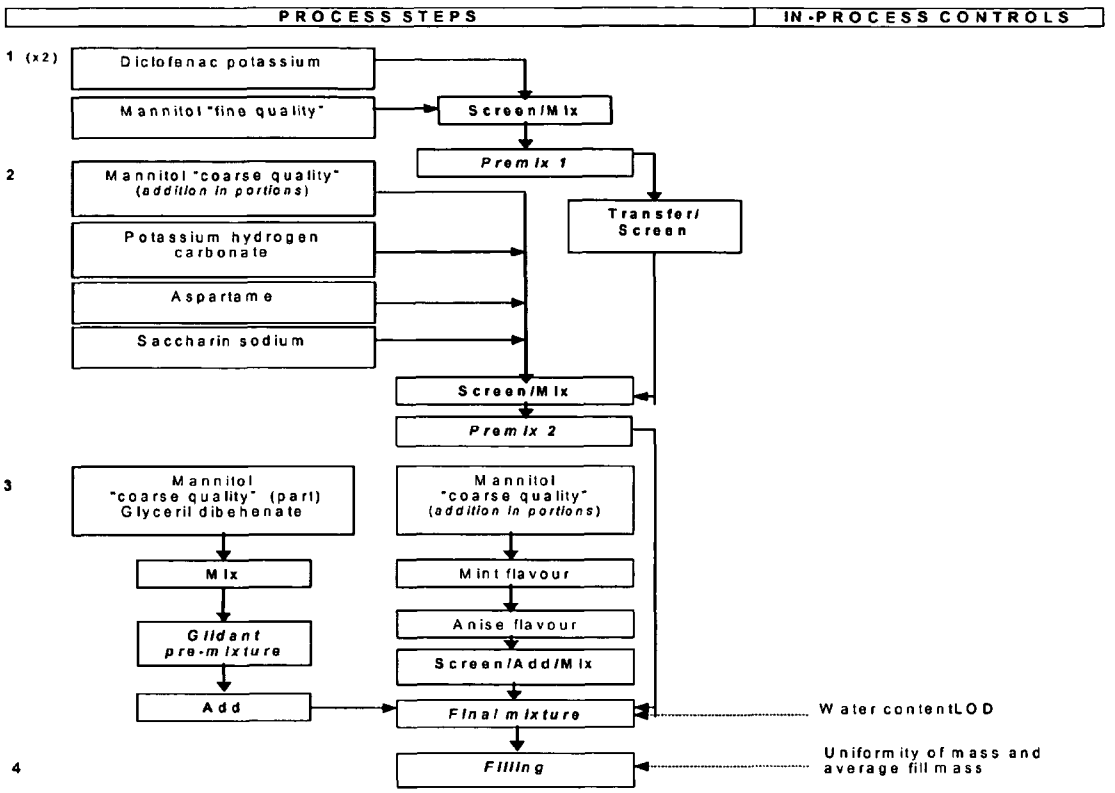
PROCESS STEPS
IN-PROCESS CONTROLS
1 (x2)
Diclofenac potassium
Mannitol "fine quality"
Screen/Mix
Premix 1
2
Mannitol "coarse quality" (addition in portions)
Transfer/ Screen
Potassium hydrogen carbonate
Aspartame
Saccharin sodium
Screen/Mix
Premix 2
3
Mannitol "coarse quality" (part) Glyceril dibehenate
Mannitol "coarse quality" (addition in portions)
Mix
Mint flavour
Glidant pre-mixture
Anise flavour
Screen/Add/Mix
Add
Final mixture
Water contentLOD
4
Filling
Uniformity of mass and average fill mass

FIG 1

DICLOFENAC FORMULATIONS AND METHODS OF USE

RELATED APPLICATIONS

This application claims priority under 35 U.S.C. §119(e) to U.S. Provisional Patent Application Nos. 60/692,024 (filed Jun. 17, 2005), and 60/691,757 (filed Jun. 17, 2005).

FIELD OF THE INVENTION

This invention concerns methods and formulations for treating migraine and other acute pain episodes using diclofenac, and formulations of diclofenac that provide both rapid and sustained relief from acute pain. The invention further concerns methods and formulations for treating symptoms that often accompany migraine and acute pain such as rebound headache, photophobia, phonophobia, nausea and vomiting.

BACKGROUND OF THE INVENTION

Diclofenac is a non-steroidal anti-inflammatory drug ("NSAID") known chemically as [(2,6-dichloro-anilino)-2-phenyl]-2-acetic acid. The drug was developed in the 1960s by scientists at Ciba-Geigy and is sold around the world by Novartis under various trade names, including Cataflam® and Voltaren® in the United States. A wet granulated formulation of diclofenac potassium was recently developed to provide an increased rate of absorption, and its pharmacokinetic properties tested against commercially available diclofenac potassium tablets. (Reiner et al., Increased absorption rate of diclofenac from fast acting formulations containing its potassium salt. Arzniem.-Forsch./Drug Res. 2001; 51:885-890.) According to the authors, the granular formulation showed a higher C_{max} than the diclofenac potassium tablets, a shorter t_{max} (i.e. time to C_{max}) and a similar AUC when compared to the tablet form.

Owing to its excellent analgesic properties, diclofenac is widely used for treating various types of pain, including both chronic and acute painful episodes. The drug is administered for the treatment of musculoskeletal and joint disorders such as rheumatoid arthritis, osteoarthritis, and ankylosing spondylitis; periarticular disorders such as bursitis and tendonitis; soft tissue disorders such as sprains and strains, and other painful conditions such as renal colic, acute gout, dysmenorrhoea, and following some surgical procedures. (Martindale (2000) Diclofenac. In: Reynolds, The Extra Pharmacopoeia. London: The Pharmaceutical Press; p. 31-33.) Diclofenac has also been studied for the treatment of headache pain from migraine attacks, using various doses and dosage forms, including 75 mg. intramuscular injections (Del Bene et al., Intramuscular treatment of migraine attacks using diclofenac sodium: a cross-over trial. J. Int. Med. Res. 1987; 1544-8), 100 mg. suppositories (Del Bene et al., Migraine attack treatment with diclofenac sodium. Cephalalgia 1985; 5:144-5), and 50 mg. enteric coated tablets. (Massiou et al., Effectiveness of oral diclofenac in the acute treatment of common migraine attacks: a double blind study versus placebo. Cephalalgia 1991; 1:59-63.)

Migraine attacks manifest a diverse array of symptoms that must be resolved in order for a treatment to be deemed truly effective against migraine (instead of just treating the symptoms). In particular, the treatment must be effective against the pain, photophobia, phonophobia and nausea that are caused by migraine, and it must be effective within the first two hours of treatment, in order to be considered a true

treatment for migraine. None of the studies reported to date suggests that a 50 mg. diclofenac product could treat all of these symptoms within two hours of treatment.

In 1993, investigators studied 100 mg. and 50 mg. diclofenac tablets, in comparison to placebo, and determined that both strengths were effective against migraine pain within two hours of treatment, but that only the 100 mg. strength was effective against phonophobia and photophobia within two hours. (Dahlöf et al., Diclofenac-K (50 and 100 mg.) and placebo in the acute treatment of migraine. Cephalalgia 1993; 13:117-123). In 1999, a separate group of investigators tested 50 mg. and 100 mg. sugar coated tablets of diclofenac potassium to treat migraine, and once again confirmed the ability of both doses to relieve migraine pain within two hours of treatment. (The Diclofenac-K/Sumatriptan Migraine Study Group, Acute treatment of migraine attacks: efficacy and safety of a nonsteroidal anti-inflammatory drug, diclofenac potassium, in comparison to oral sumatriptan and placebo. Cephalalgia 1999; 19:232-40.) The investigators concluded that neither dose was effective against photophobia two hours after treatment, that both doses were effective against photophobia eight hours after treatment, that only the 100 mg dose was effective against phonophobia two hours after treatment, and that the 50 mg dose was effective against photophobia eight hours after treatment.

The 1999 investigators also studied the effectiveness of 100 mg and 50 mg. diclofenac-K immediate release tablets at preventing recurrence of headaches within 48 hours of treatment. The investigators concluded that patients treated with the 50 mg and the 100 mg diclofenac-K tablets actually had a higher incidence of headache recurrence than patients treated with placebo (i.e. that the diclofenac-K performed worse than placebo), although the statistical significance of these findings is not reported.

This latter finding is consistent with other recent literature which recommends the use of a "long acting NSAID" to reduce the frequency of rebound headaches. For example, Plachetka recommends in U.S. Pat. No. 6,586,458 that triptan therapy be augmented with a "long acting NSAID" to provide "a substantial reduction in the frequency [of] relapse of headaches." Diclofenac potassium is not considered a long acting NSAID because it displays an average C_{max} within only about one hour and a terminal half life of only about 1.9 hours when administered in commercially available sugar coated tablets.

Diclofenac is generally taken orally in the form of normal tablets or tablets covered with coatings resistant to gastric juices, or rectally, or by injection, or topically. Recently, however, in WO 97/44023, Reiner et al. proposed to administer diclofenac in a number of less conventional dosage forms—including as a powder sachet for oral administration after dissolving in water—for quicker onset of analgesic relief. One of the primary obstacles in the manufacture of powder sachets is the distribution of the drug in the powder, and the uniformity of content in the finished product. These hurdles are magnified in the production of diclofenac sachets due to the poor aftertaste of diclofenac, and the need to incorporate additional ingredients to compensate for this poor taste.

To ensure an adequately homogenous distribution of drug product in the bulk powder, Reiner et al. disclose a wet granulation process for manufacturing the powder sachets. In the first step of the process, a wet granulate is prepared from diclofenac potassium, potassium bicarbonate, saccharin, aspartame and mannitol, using 95% ethanol as the wetting

agent. The granulate is then mixed with over one gram of sugar (saccharose) and various flavoring agents to improve the taste of the composition.

The method described by Reiner et al. produces an excellent pharmaceutical dosage form but suffers from a number of disadvantages including the size of the sachet (2 g) which makes the sachet more difficult to dissolve, and the presence of sugar in the formulation, which should be avoided in the diabetic population. In addition, the process requires precise controls on the granulometric process to assure uniform distribution of drug in the granulate and consistent amounts of drug in the finished product. What is needed is an alternative method for producing sugar-free powder diclofenac sachets and other fast acting dosage forms of diclofenac.

SUMMARY OF INVENTION

The inventors have unexpectedly discovered that rapidly bioavailable formulations of diclofenac are effective in the treatment of migraine and other acute pain episodes, and that in spite of their quick onset of action, they provide sustained relief against acute pain for up to twenty-four hours. Contrary to the prior art, which suggests that a long acting NSAID should be used to prevent rebound headache, and that a rapidly bioavailable formulation of diclofenac would be ineffective against rebound headache, the inventors have discovered that a rapidly bioavailable formulation of diclofenac, as measured by t_{max} and C_{max}, prevents recurrence of headaches for at least twenty four hours after treatment in a significant population of migraine sufferers. In addition, the consistency of bioavailability seems to improve as the bioavailability of the molecules becomes more rapid, which further contributes to the clinical efficacy observed for these formulations.

The inventors have also surprisingly discovered that these rapidly bioavailable formulations relieve symptoms often associated with migraine and other acute pain, including photophobia and phonophobia, better than conventional immediate release tablets. These results are surprisingly seen even though the diclofenac in these formulations is more rapidly eliminated from the bloodstream than conventional immediate release tablets of diclofenac, and even though the total amount of diclofenac absorbed in the blood stream (measured as the area under the curve (i.e. $AUCO_{0-\infty}$)) is comparable for the two formulations. The formulations are thus able to meet all of the primary clinical endpoints for evaluating migraine treatments, and for completely treating migraine.

Therefore, in one embodiment the invention preferably provides a method of treating migraine comprising: (a) providing a liquid formulation comprising 50 mg. of diclofenac or a pharmaceutically acceptable salt thereof, wherein said formulation: (i) is provided as a unit dose powder formulation and dissolved or suspended in water immediately before administration, or as a unit dose liquid formulation that is ingested with or without further mixing; (ii) achieves t_{max} in from about 10 to about 20 minutes; and (iii) optionally but preferably achieves a C_{max} of from about 1500 to about 2500 ng/ml; and (b) orally administering said formulation to a patient suffering from migraine, wherein migraine is defined as a disease manifested in a population of patients by periodic attacks of headache pain, nausea, photophobia and phonophobia. In one particular embodiment the method is used to treat migraine that is accompanied by photophobia and/or phonophobia. In another particular embodiment, the method is used to treat migraine patients who suffer from recurrent headache, and are diagnosed as requiring relief from recurrent headache within twenty-four hours of the initial treatment.

In other embodiments the method is used to treat any episode of acute pain in which the pain would otherwise persist for at least about eight hours, and pain relief is required for this time period. Thus, in still another embodiment the invention preferably provides a method of treating acute pain in a human patient requiring pain relief for at least eight hours, comprising: (a) providing an oral formulation comprising about 50 mg. of diclofenac or a pharmaceutically acceptable salt thereof, wherein said formulation (ii) achieves t_{max} in from about 10 to about 35, 30, or 25 minutes; and (iii) optionally but preferably achieves a C_{max} of from about 1400 or 1500 to about 2500 ng/ml; and (b) orally administering said formulation to a patient suffering from acute pain, preferably no more than 3 total times in a 24 hour period.

In still another embodiment the invention provides an alternative method for preparing powder diclofenac sachets that is based predominantly on the large proportion of mannitol in the formulation, which preferably includes a precise control of particle size of diluents in the finished product. The large proportion of mannitol imparts surprisingly rapid bioavailability to the formulation, while the control of particle size assures uniform distribution of diclofenac in the material used to fill the sachets and consistent amounts of drug in each sachet without the use of sugar or large amounts of diluent as taught in the prior art. The method and powders produced by the method are characterized by, among other variables, (1) the ratio of the diluent to the diclofenac in the powder, (2) a combination of particle sizes of the diluent in the final composition, and (3) the sequence of mixing the diclofenac and the varying particle sizes of diluent.

The invention further provides methods for manufacturing highly concentrated liquid formulations of diclofenac that can be drawn as drops from a bottle and administered after mixing the diclofenac with a suitable carrier such as water. In one aspect of this embodiment the invention provides a method of making a liquid solution of diclofenac, wherein the diclofenac is present in the liquid at a concentration of from about 10 to about 100 mg./ml., comprising (a) dissolving diclofenac in ethyl alcohol to form a solution, (b) mixing said solution with glycerol to form a second solution, and (c) mixing said second solution with water.

Additional advantages of the invention will be set forth in part in the description which follows, and in part will be obvious from the description, or may be learned by practice of the invention. The advantages of the invention will be realized and attained by means of the elements and combinations particularly pointed out in the appended claims. It is to be understood that both the foregoing general description and the following detailed description are exemplary and explanatory only and are not restrictive of the invention, as claimed.

DETAILED DESCRIPTION OF THE DRAWING

The accompanying drawing, which is incorporated in and constitutes a part of this specification, illustrates several embodiments of the invention and together with the description, serves to explain the principles of the invention.

FIG. **1** is a flow diagram illustrating a non-granulate method and sequence of mixing employed in making 900 mg. powder sachets of the instant invention that contain 50 mg. of diclofenac potassium.

DETAILED DESCRIPTION OF THE INVENTION

The present invention may be understood more readily by reference to the following detailed description of preferred embodiments of the invention and the Examples included therein.

Methods of Treating Migraine and Acute Pain

As discussed above, the invention provides novel formulations of diclofenac—especially diclofenac potassium—that have proven to be remarkably effective against migraine headache and other forms of acute pain. The formulations may contain various quantities of diclofenac, in various oral dosage forms, ranging from about 12.5 mg. to about 100 mg. of diclofenac or a pharmaceutically acceptable salt thereof. Thus, for example, the formulation can contain about 12.5, 25, 37.5, 50, 75 or 100 mg of diclofenac or a pharmaceutically acceptable salt thereof, in a tablet, a capsule, a powder for oral solution, an oral solution or suspension, on orally dissolving tablet, a mucoadhesive film, or any other orally ingestable dosage form. In a particularly preferred embodiment, however, the formulations of the present invention are present in a liquid form when ingested, and they contain about 50 mg. of diclofenac or a pharmaceutically acceptable salt thereof. In another preferred embodiment, the formulations are used to treat migraine headache.

Therefore, in one embodiment the invention provides a method of treating migraine comprising: (a) providing a liquid formulation comprising 50 mg. of diclofenac or a pharmaceutically acceptable salt thereof, wherein said formulation: (i) is provided as a unit dose powder formulation and dissolved or suspended in water immediately before administration, or as a unit dose liquid formulation that is ingested with or without further mixing; (ii) achieves t_{max} in from about 10 to about 20 minutes; (iii) optionally but preferably achieves a C_{max} of from about 1500 to about 2500 ng/ml; and (b) orally administering said formulation to a patient suffering from migraine, wherein migraine is defined as a disease manifested in a population of patients by periodic attacks of headache pain, nausea, photophobia and phonophobia.

In one particular embodiment, the methods of this invention are used to treat some of the most difficult to treat migraine patients—i.e. those whose headache pain is likely to recur within twenty-four hours of initial treatment, or those who also suffer from photophobia or phonophobia. Therefore, in another embodiment the invention provides a method of treating migraine in a human patient suffering from migraine comprising: (a) providing a liquid formulation comprising about 50 mg. of diclofenac or a pharmaceutically acceptable salt thereof, wherein said formulation: (i) is provided as a powder formulation and dissolved or suspended in water immediately before administration, or as a liquid formulation that is ingested with or without further mixing; (ii) achieves t_{max} in from about 10 to about 20 minutes; (iii) optionally but preferably achieves a C_{max} of from about 1500 to about 2500 ng/ml; and (b) diagnosing a patient suffering from migraine as requiring sustained migraine relief for at least 24 hours (such as a patient who is susceptible to rebound or recurrent headaches); and (c) orally administering said formulation to said patient.

Patients who are particularly well-suited for treatment by the methods of this invention are those patients who have previously been treated for migraine pain using an acute pain medication, but who continued to suffer from symptoms such as phonophobia, photophobia, nausea and vomiting, especially those individuals who required additional medication for these symptoms. Thus, for example, in one embodiment the patient has previously been diagnosed as requiring relief from photophobia, phonophobia, nausea or vomiting in conjunction with treatment for migraine pain. In another embodiment the method is performed without administering other medications for the relief of photophobia, phonophobia, nausea or vomiting. In still another embodiment the method is performed without administering other medications for the relief of migraine pain.

Therefore, in still another embodiment the invention provides a method of treating migraine associated with phonophobia or photophobia in a human patient comprising: (a) providing a liquid formulation comprising 50 mg. of diclofenac or a pharmaceutically acceptable salt thereof, wherein said formulation: (i) is provided as a powder formulation and dissolved or suspended in water immediately before administration, or as a liquid formulation that is ingested with or without further mixing; (ii) achieves t_{max} in from about 10 to about 20 minutes; (iii) optionally but preferably achieves a C_{max} of from about 1500 to about 2500 ng/ml; and (b) orally administering said formulation to a patient suffering from migraine associated with photophobia or phonophobia.

As discussed above, this invention also concerns methods for treating acute pain using diclofenac, and formulations of diclofenac that provide immediate and sustained relief from any type of acute pain. In addition to migraine headache pain, the pain may derive from a variety of sources, including musculoskeletal and joint disorders such as rheumatoid arthritis, osteoarthritis, and ankylosing spondylitis, periarticular disorders such as bursitis and tendonitis, soft tissue disorders such as sprains and strains, and other painful conditions such as renal colic, acute gout, dysmenorrhoea, and following some surgical procedures. In one preferred embodiment the acute pain is post-operative pain, such as post-operative dental pain.

The formulations are particularly well suited for providing relief from sustained acute pain, defined herein as acute pain that would otherwise persist for about 4, 6 or 8 hours without the treatment contemplated by the current invention. In one preferred embodiment the patient treated by the method has been previously diagnosed as requiring relief from sustained acute pain. A patient requiring sustained relief from acute pain is a patient who has either been previously diagnosed as requiring rescue medication within about 4, 6 or 8 hours of treatment for said acute pain, or a patient whose acute pain is expected to persist for 4, 6 or 8 or more hours in the absence of treatment.

In another embodiment, therefore, the invention provides a method of treating acute pain in a human patient requiring pain relief for at least eight hours, comprising: (a) providing an oral formulation comprising about 50 mg. of diclofenac or a pharmaceutically acceptable salt thereof, wherein said formulation: (i) achieves a C_{max} of from about 1400, 1450 or 1500 to about 2500 ng/ml; and (ii) achieves t_{max} in from about 10 to about 35, 30 or 25 minutes; and (b) orally administering said formulation to a patient suffering from acute pain, preferably no more than 3 total times in a 24 hour period.

The sustained relief provided by the compositions of the present invention provides numerous advantages in the treatment of acute pain, and leads to decreased requirements for pain medication by many patients. Thus, in one embodiment the method is performed without administering other immediate pain relief or rescue medications within the first 4, 6 or 8 hours of administering the diclofenac formulation. In one embodiment, the formulation is administered no more than 3 total times in a 24 hour period. In another embodiment, the formulation is administered as needed for pain every 2, 4, 6 or

8 hours (or every 4-6, 4-8, or 6-8 hours), as needed for pain, preferably not to exceed three times per day. In yet another embodiment, the formulation is administered once every eight hours.

As discussed above, the formulations of the present invention are preferably administered as a liquid for oral ingestion, and can be provided in any form suitable for such administration. In a particularly preferred embodiment, the formulation is provided in a single unit dose as a powder sachet, which is mixed with water before administration. In other embodiments the formulation is already dissolved in a liquid, as in the drop formulation of the present invention and the unit dose vials discussed elsewhere herein. It will be understood, however, that the relief from migraine and acute pain occasioned by the methods of the present invention can be achieved with any oral formulation that achieves the pharmacokinetics described herein, and that the invention extends to any such dosage form.

Statistically Significant Relief

In some embodiments of the present invention, the medication is administered to a plurality of patients suffering from migraine, and statistically significant relief is observed based on one or more primary or secondary clinical endpoints, in comparison to placebo or 50 mg. immediate release diclofenac potassium tablets (i.e. Cataflam), including:

- two hour pain relief (i.e. a decrease in pain intensity from moderate/severe to mild/none)
- pain free at two hours
- sustained pain relief for 6, 8 or 24 hours
- relief from phonophobia at two hours
- relief from photophobia at two hours
- relief from nausea and vomiting at two hours

As noted above, the ability to attain statistically significant relief by the methods of the present invention is greatly influenced by the coefficients of variation in Cmax and tmax observed for this invention, which seem to decrease as the diclofenac in these formulations becomes more bioavailable.

Of course, every patient treated by the methods of the present invention will not require relief from every clinical endpoint, or obtain relief from every clinical endpoint. In addition, the plurality of patients that any individual physician or physician's practice group treats may not rise to the level of "statistical significance," as that term is typically used in the pharmaceutical industry (i.e. $p<0.05$). In the context of this invention, the term "statistically significant" is not based solely upon the plurality of patients treated by the defined method, but takes into account well designed comparative clinical trials versus placebo that have previously been conducted to confirm the statistically significant relief, in addition to the clinical results obtained by practice of the present invention by individual patients, practitioners, or physician practice groups.

Pharmacokinetics

In one embodiment the composition is characterized by its pharmacokinetics, such as C_{max} (i.e. average concentration of active chemical in the bloodstream after oral ingestion, preferably in the fasted state), and its t_{max} (i.e. average time to reach said C_{max}, in a fasted state). In a particularly preferred embodiment, the mean C_{max} for a 50 mg. diclofenac composition ranges from about 1300, 1400, 1500, 1600 or 1700 to about 2600, 2500, 2300, 2100, 2000 or 1900 ng/ml. A suitable range can be derived from any of these upper and lower bounds, but in one embodiment the formulation preferably attains a C_{max} of from about 1300, 1400 or 1500 to about 2500 ng/ml; or from about 1500, 1600, or 1700 to about 2100 ng/ml, for a 50 mg. diclofenac formulation. It will be understood, of course that any of these C_{max} values can be normalized based on the dose administered. Thus, for example, a 1500 ng/ml C_{max} observed for a 50 mg. dose could be normalized to 30 ng/ml·g and applied to other dose amounts. In a particularly preferred embodiment the formulations yield only one peak concentration when blood concentrations are plotted against time.

The median t_{max} (i.e. time to reach C_{max}) of the formulations is preferably from about 5 or 10 to about 40, 35, 30, 25 or 20 minutes. Once again, a suitable range can be derived from any of these upper and lower bounds, but in one particular embodiment the t_{max} of the formulation is most preferably from about 10 to about 35 minutes, from about 10 to about 30 minutes, from about 10 to about 25 minutes, or from about 10 to about 20 minutes. The inter-subject coefficient of variability for said C_{max} preferably is less than about 70, 65, 60, 55, 50, 40 or 35%, and the inter-subject coefficient of variability for said t_{max} is preferably less than about 70, 60, 50, 40 or 35%.

Of course, it will be understood that bioavailability can differ from different study sites. When a single formulation gives results that vary significantly among different clinical sites and investigators, the results can be proportionately normalized against the bioavailability of Cataflam tablets, based upon the results reported in the examples hereto. Thus, for example, if the C_{max} that a laboratory observes for Cataflam is only 750 ng/ml, all of the C_{max} results reported from the laboratory could be adjusted by a factor of (1037.124)/(750).

Methods of Formulation

As noted previously, the invention also concerns methods of making a particulate flowable diclofenac composition that can be defined by a number of characteristics, including the presence of a fine powdered diluent, the combination of fine and coarse diluent, the total amount of diluent, the size distribution of diclofenac particles, or the use of a non-hygroscopic diluent. These various features and aspects of the present invention are set forth in greater detail below.

Diclofenac

The diclofenac used in the present invention can be defined by various parameters. In one embodiment, the raw material will be a powder that exhibits no more than 0.5 wt. % loss on drying. In another embodiment not less than 90% of the diclofenac particles are less than 500 micrometers in diameter, not less than 40% and not more than 70% of the particles are less than 200 micrometers in diameter, not less than 35% and not more than 65% of the particles are less than 150 micrometers in diameter, and not less than 30% of the particles are less than 100 micrometers in diameter. (Analyses performed using sieves according to the Sieve Test 2.9.12 Eur.Ph.—Alpine Air Jet Sieve.) The average particle size for the diclofenac powder is preferably about 150, 160, 170, 180, 190, 200, 210, 220, 230, or 240 micrometers, and can range between any two of the foregoing variables (i.e. from about 150 to about 230 micrometers, or from about 170 to about 220 micrometers).

The diclofenac can be present in acid or salt form although, owing to its poor solubility in water, diclofenac is normally used in salt form. The salts of diclofenac customarily used are those of sodium, potassium or other alkali and alkaline earth metals, together with salts of organic nature, such as the salts of basic amino acids, such as lysine, arginine and ornithine, or other pharmacologically acceptable organic bases which have the ability to render the resulting salt soluble in water. Diclofenac potassium is preferably used in this invention due to its fast onset of action.

In a preferred embodiment, 50 mg. of diclofenac or its salt is used in the final dosage form, although other amounts could be used including 12.5, 25, 37.5, 50, 75 or 100 mg of diclofenac, or a range having as endpoints any of the foregoing amounts. The amount of diclofenac preferably does not vary by more than about 95-105% from dose to dose.

Buffering Agents

Buffering agents are not critical to the invention, but are preferably used to provide a rapid rate of onset for the final pharmaceutical product. In a preferred embodiment for powder sachets, the buffering agent controls the pH of the formulation when dissolved in water, and preferably yields a pH greater than about 6.8, 7.0, 7.2, or 7.4, and less than about 7.8, 7.7 or 7.6, when mixed with 50 ml or 100 or 200 ml. of water at 25 degrees Celsius.

Particularly preferred buffering agents are alkali metal carbonates and bicarbonates and these agents are preferably employed in a weight ratio relative to the diclofenac of greater than about 1:5, 2:5, 2:1, 3:1 or 5:1. If desired, an upper limit on the buffer:diclofenac ratio can be placed at about 20:1, 10:1, 5:1, 1:1, 4:5 or 3:5. Ranges can be selected from any two of the foregoing values that are mathematically possible. In a preferred embodiment, the buffer:diclofenac weight ratio ranges from about 1:5 to about 4:5. Particularly preferred alkali metal bicarbonates are sodium bicarbonate and potassium bicarbonate.

Final Powdered Sachet Product

The powder sachets used in the methods of this invention can be produced by various methods including dry granulation, wet granulation and dry admixing processes. A suitable product produced by wet granulation is described, for example, by Reiner et al. in WO 97/44023.

In one clinical trial, a representative 50 mg. diclofenac formulation obtained by the method disclosed in examples 3 and 4 was shown to exhibit the following pharmacokinetic properties:

C_{max} mean value	1620 ng/ml (CV = 53.8%)
t_{max} mean value	13.98 min (CV = 32.2%)
AUC 0-t mean value	1010 (CV = 42.4%)

In contrast, a 50 mg. formulation prepared by the wet granulation process disclosed in WO 97/44023 has been shown to exhibit the following pharmacokinetic properties:

C_{max} mean value	2213 ng/ml (CV = 33.57%)
t_{max} mean value	13.68 min (CV = 16.3%)
AUC 0-t mean value	1332.99 (CV = 26.86%)

In one embodiment the powdered sachet is produced by a dry mixing process and is characterized by the presence of diclofenac particles having one of the particle size distributions described above. In another embodiment the product is characterized by the total amount of powder used to fill a sachet, which is preferably greater than 500, 600, 700 or 800 mg., and/or less than 1800, 1600, 1400, 1200, or 1000 mg., based on a 50 mg. diclofenac sachet. A preferred amount of powder is 900 mg. and the amount preferably does not vary outside the 855-945 mg/sachet range per package.

In still another embodiment the invention is characterized by the solubility of the product in water, the amount of water required to solubilize the product, and the time required to solubilize the product in a given amount of water. Therefore, in one embodiment a unit dose of the sachet is greater than 75% or 85% soluble or is completely soluble in 50 ml. of water at 25 degrees Celsius. In another embodiment the unit dose is greater than 75% or 85% solubilized or is completely solubilized in 50 ml. of water with stirring at 25 degrees Celsius in less than 5 minutes. This optimized solubility seems to restrict absorption to a shorter part of the gastrointestinal tract, most likely contributing to the faster absorption rate and to the lower variability in the absorption compared to immediate release diclofenac potassium tablets.

The water content of the final product is preferably less than about 1.5%. The final product is also preferably free of sugar (saccharose), preferably includes as sweeteners aspartame and/or saccharin, and preferably includes as flavoring agents anise and/or mint.

Practically any container that maintains hermetic conditions could be used for packaging the powder sachets, though preferably the container consists of a sachet that is hermetically sealed in four directions to maintain the product in hermetic conditions during storage. The sachet is preferably made from a three-layer coupled paper/aluminum/polyethylene foil in which the weight of the paper is from about 0.475 to about 0.525 g/100 cm^2, the weight of the aluminum is from about 0.203 to about 0.229 g/100 cm^2, and the weight of the polyethylene is from about 0.295 to about 0.365 g/100 cm^2.

Diluents for Powder Sachets

Diluents or "filler excipients" are prefereably added to increase the resulting dosage units' bulk, and to improve blending characteristics. Freely soluble diluents are particularly preferred because they improve the solubility of the final product. The diluent preferably has a solubility in water at 25 degrees Celsius of greater than about 10, 15 or 20 g/100 ml. of water. A particularly preferred diluent is mannitol, which is substantially non-hygroscopic, and which has a solubility in water of 22 g/100 ml. Other suitable diluents include lactose, glucose, sucrose, xylitol, and especially lactilol monohydrate due to its beneficial non-hygroscopic properties.

The size of the diluent, and the order of adding the diluent during the mixing process, have also proven important in the practice of the present invention. In a preferred dry mixing process, the diclofenac is mixed with a fine diluent powder before any further processing to distribute the diclofenac and to preserve its flowability. In a preferred wet granulation method, the diclofenac is granulated along with coarse diluent powder before any further processing.

The particles sizes for two exemplary fine diluent powders are reported below:

Powder 1 (preferred)	Powder 2
Size Distribution (measured by laser)	
>250 μm: not more than 5%	>500 μm: not more than 10%
>100 μm: not more than 25%	>315 μm: not more than 25%
>20 μm: not less than 55%	>40 μm: not less than 60%
Size Distribution (measured with sieves)	
>150 μm not more than 2%	>250 μm not more than 10%
Average Particle Size (measure by laser)	
50 micrometers	160 micrometers

The fine diluent powder can also be characterized by its average particle diameter, which can range from less than about 200, 180, 160, 140, 120, 100, or 80 micrometers, to

greater than about 1, 5, 10, 20, 30 or 40 micrometers, with ranges defined between any two of the foregoing values. Most preferably, the fine diluent powder has an average particle size of about 50±40, 30, 20 or 10 micrometers.

As a still further alternative, the fine diluent can be characterized by its particle size relative to the diclofenac powder. In such an embodiment, the fine diluent is characterized by an average particle size of less that 100%, 80%, 60% or 40% of the average particle size of the diclofenac powder, and greater that about 5%, 10% or 20% of the average particle size of the diclofenac powder, again with ranges defined between any two of the foregoing values.

In a 50 mg. diclofenac sachet, the weight ratio of fine diluent to diclofenac in the final powder composition is preferably greater than about 1:5, 1:2, 1:1 or 1.2:1, and/or less than about 10:1, 6:1, 4:1, 3:1 or 2:1, with ranges defined between any two of the foregoing values. A preferred range of weight ratios is from about 1:1 to about 2:1. In a particularly preferred embodiment for a 50 mg. diclofenac sachet, the sachet comprises from about 50 to about 100 mg. of the fine diluent particles, from about 60 to about 85 mg. of fine diluent particles, or from about 70 to about 75 mg. of fine diluent particles.

Once the initial mixture of diclofenac and fine diluent powder is prepared in the preferred dry mixing process, a coarser diluent is preferably used to mix in the remaining components, preferably using a step-addition process in which successive amounts of the coarser diluent are added between each newly added ingredient. A preferred sequence of mixing, for the dry blending and wet granulation processes, is set forth in the examples hereto. As with the fine diluent, the coarser diluent is also preferably non-hygroscopic. In a preferred embodiment, the coarser diluent is the same chemical entity as the fine diluent powder, which is preferably mannitol. In one embodiment the coarse diluent is characterized by an average particle size that is greater than the average particle size of the fine diluent, and preferably has an average particle size greater than about 120%, 150% or 200% of the average particle size of the fine diluent, and less than about 1000%, 800% or 600% of the average particle size of the fine diluent, with ranges defined between any two of the foregoing values.

In an alternative embodiment the coarse diluent is defined by its particle size relative to the particle size of the diclofenac powder. In this embodiment, the coarse diluent preferably has an average particle size from about 60, 80 or 100% to about 1000, 800, 600, 400 or 200% of the average particle size of the diclofenac powder, with ranges defined between any two of the foregoing variables.

In a still further alternative, the coarse diluent can be characterized as having an average particle diameter of greater than about 75, 85, or 100 micrometers, and less than about 300, 250, 200, or 150 micrometers. In a particularly preferred embodiment, the coarse diluent powder has the following size distribution:

>315 μm: not more than 10%

>75 μm: not less than 90%

The amount of the coarse diluent is not critical, though it is typically added in an amount to bring the total sachet weight up to about 900 mg. in a 50 mg. diclofenac formulation. The total dosage form preferably comprises from about 200 to about 1500 mg., from about 400 to about 1000 mg., from about 500 to about 800 mg., or from about 600 to about 750 mg. of coarse diluent in a 50 mg. diclofenac sachet. In various embodiments, the weight ratio of coarse diluent to diclofenac in a 50 mg. diclofenac sachet is greater than about 2:1, 4:1, 6:1, 8:1 or 10:1, and less than about 40:1, 30:1, 20:1 or 15:1. A preferred range of weight ratios of the coarse diluent powder to the diclofenac in a 50 mg. diclofenac sachet is from about 10:1 to about 20:1.

The invention can also be defined by the total amount of non-hygroscopic diluent (fine and coarse) relative to the amount of diclofenac and, in various embodiments for a 50 mg. diclofenac sachet, the weight ratio is greater about 1.5:1, 2:1, 4:1, 6:1, 8:1, 10:1, or 12:1, and less than about 80:1, 60:1, 40:1, 30:1, 25:1 or 20:1. In other embodiments, the total weight of the non-hygroscopic diluent is greater than about 40%, 50%, 60% or 70%, and less than about 95%, 90% or 85% of the weight of the total composition in the sachet.

Alternative Doses and Diluent/Diclofenac Ratios

As discussed above, the foregoing weight ratios and relative quantities of diclofenac to fine diluent, coarse diluent and total diluent are given for a 50 mg. dilofenac sachet, preferably in a 900 mg. formulation. It will be understood that the total volume of the sachet can be divided or increased by various factors, such as 1.5, 2 or 4 while maintaining the foregoing weight ratios, to lower or increase the total amount of the diclofenac in the formulation. Thus, for example, a 900 mg. sachet containing 50 mg. of diclofenac potassium, 648 mg. of coarse diluent and 73 mg. of fine diluent, could be divided in two to provide a 450 mg. sachet containing 25 mg. of diclofenac potassium, 324 mg. of coarse diluent, and 36.5 mg. of fine diluent, or it could be divided in four to provide a 225 mg. sachet containing 12.5 mg. of diclofenac, 162 mg. of coarse diluent and 18.25 mg. of fine diluent.

It is also possible to simply divide the 50 mg. of diclofenac in the sachets described above in half, and provide 25 mg. diclofenac sachets while keeping the amounts of fine and coarse diluent substantially constant by, for example, basically doubling the ratios of fine diluent and coarse diluent to diclofenac reported above. Thus, for example, one could prepare 25 mg. of diclofenac in a 900 mg. sachet using substantially the same amounts of fine and coarse diluent as reported above, simply by dividing the total diclofenac in the formulation by two. Once again, the total volume of such a sachet could be divided or increased by various factors, such as 1.5, 2 or 4 while maintaining the revised weight ratios, to lower or increase the total amount of the diclofenac in the formulation.

Lubricants for Powder Sachets

While the use of lubricants is not strictly necessary, in a preferred embodiment they are added to the powder to prevent the powder from sticking to the metering machine in the final stage of filling the sachets. Suitable lubricants include magnesium stearate, stearic acid, hydrogenated castor oil, talc, or mixtures thereof, but a preferred lubricant is glycerol dibehenate. The lubricant is preferably present in an amount of from about 0.01 to about 2 wt. %, and preferably about 0.2% w/w, based on the weight of the powder composition.

In the method of manufacturing the product, the lubricant is preferably mixed with the diclofenac/fine diluent mixture as a separately prepared premix that also comprises diluent, albeit in a coarser particle size.

Powder Sachet Processing

In a preferred embodiment the powder sachets used in the invention are made by a dry blending process in which the diclofenac powder and other ingredients are added sequentially to successive batches of diluent. In a particularly preferred embodiment, the diclofenac is first blended with the fine diluent followed by the successive addition of coarse particulate and further inactive ingredients.

Therefore, in one embodiment the diclofenac composition is a particulate flowable diclofenac composition made by a

process comprising: (a) mixing powdered diclofenac with a fine powdered diluent to form a first mixture; and (b) mixing said first mixture with a coarse powdered diluent to form a second mixture. The second mixture is preferably obtained by adding the first mixture to a predefined volume of the coarse diluent, which has preferably been pre-loaded into a mixing machine. In a further embodiment the method of making the composition additionally comprises:

a) mixing said second mixture with an alkali metal bicarbonate to form a third dry mixture;

b) mixing said third mixture with coarse diluent to form a fourth mixture;

c) mixing coarse diluent with a lubricant to form a fifth mixture; and

d) mixing said fourth and fifth mixtures.

While the preferred method of manufacturing the compositions of the present invention is dry blending, other methods can also be employed that do not depend on mixing of dry powders including wet granulation. For wet granulation, the binder can be added dry to the powder blend, or as a solution in the solvent. The solvent is usually ethanol, water, or a mixture of both. The actual granulation is performed in either a high-shear, or low-shear type mixer. Low-shear granulation requires cheaper equipment and produces a more porous granule. High-shear granulation is faster and affords good control over particle size.

Fluid bed wet granulation is a variation of the process in which the granulation and drying is carried out in the same vessel (a fluid bed granulator). The powder mix is fluidized by dry air inside a chamber. The binder solution is sprayed onto the fluidized powder to form the agglomerates. Air fluidizing continues until the agglomerates are dry. The process requires expensive equipment, but is simpler and produces a very porous low-density granule, which can result in faster drug dissolution. Slow drug dissolution is sometimes a problem associated with wet granulation, as the active ingredient is locked into the granule, and initial tablet disintegration liberates the granules rather than the primary drug particles.

In dry granulation, particle size enlargement is achieved by aggregating the powder particles under high pressure (i.e., by compaction) then milling the compressed material to the desired size. Fines generated by milling are recycled back through the compactor. The compression step is typically carried out in a roller compactor in which the powder is compressed between two rollers.

Therefore, in another embodiment the invention provides a method of making a wet granulated powder formulation of diclofenac comprising: (a) wet granulating an admixture of diclofenac (or a pharmaceutically acceptable salt thereof), a first portion of coarse mannitol, and a suitable bicarbonate to form a wet granulate; and (b) admixing said wet granulate with a second portion of coarse mannitol and fine mannitol. In another embodiment the invention provides a method of making a wet granulated powder formulation of diclofenac comprising: (a) wet granulating an admixture of diclofenac (or a pharmaceutically acceptable salt thereof), a first portion of mannitol and optionally a bicarbonate to form a wet granulate; and (b) admixing said wet granulate with a second portion of mannitol, wherein the weight ratio of mannitol and diclofenac in said final formulation is greater than about 1.5:1.

Further subembodiments of the foregoing principal embodiments can be defined by one or more of the following additional parameters:

the wet granulation is performed in ethanol;

the method further comprises admixing said wet granulate with glyceryl dibehenate.

the wet granulate comprises from about 8 to about 15 weight parts diclofenac (preferably 10 to 13 weight parts), from about 12 to about 20 weight parts coarse mannitol (preferably 15 to 18 weight parts); and from about 3 to about 7 weight parts bicarbonate (preferably 4 to 6 weight parts).

wet granulate including from about 8 to about 15 weight parts diclofenac (preferably 10 to 13 weight parts) is admixed with: from about 100 to about 160 weight parts coarse mannitol (preferably 120 to 140 weight parts); from about 12 to about 20 weight parts fine mannitol (preferably 14 to 18 weight parts); and from about 0.2 to about 0.7 weight parts glyceryl dibehenate (preferably 0.4 to 0.5 weight parts), preferably in sequential order while stirring.

the formulation comprises: fine mannitol and diclofenac or a pharmaceutically acceptable salt thereof at a weight ratio of from about 1:2 to about 5:1, coarse mannitol and diclofenac or a pharmaceutically acceptable salt thereof at a weight ratio of from about 2:1 to about 40:1, wherein: said fine diluent has an average particle size of from about 10 to about 180 micrometers, said coarse diluent has an average particle size of from about 85 to about 250 micrometers, and said coarse diluent has an average particle size greater than the average particle size of said fine diluent.

said mannitol comprises fine mannitol and coarse mannitol at a weight ratio of from about 1:5 to about 1:20; said fine mannitol has the following particle size distribution: 250 μm: not more than 5%; 100 μm: not more than 25%; 20 μm: not less than 55%; and said coarse diluent has the following particle size distribution: 315 μm: not more than 10%; and >75 μm: not less than 90%.

A weight ratio of mannitol to diclofenac of greater about 1.5:1, 2:1, 4:1, 6:1, 8:1, 10:1, or 12:1, and less than about 80:1, 60:1, 40:1, 30:1, 25:1 or 20:1.

Total mannitol percentage greater than about 40%, 50%, 60% or 70%, and less than about 95%, 90% or 85%, of the weight of the total composition in the sachet.

Liquid Formulations

The invention further provides methods for using diclofenac compositions that are provided as liquids having the diclofenac already dissolved therein. Practically any sort of single use "vial" can be used for containing a liquid dosage form. For purposes of this application, "vial" means a small glass container sealed with a suitable stopper and seal, or any other suitable container such as breakable and non-breakable glass and plastic vials, miniature screw-top jars, and any other type of container of a size capable of holding a small amount of diclofenac liquid. Thus, for example, when the diclofenac is formulated in liquid solutions that contain approximately 50 mg. diclofenac potassium in every ml. of liquid, the formulation can be packaged in a dropper bottle that contains any suitable quantity of liquid, typically from about 15 to about 100 ml. of solution. The concentration of diclofenac in these formulations typically will be about 50 mg/ml, but could range from about 10 to about 100 mg/ml, including 10, 25, 50, 75 and 100 mg./ml. Alternatively, the vial can be a single use vial, which would contain a suitable quantity of liquid such as about 15 ml. for a 50 mg. dose of diclofenac potassium.

As with the other formulations of this invention, buffering agents can be used in the drop formulations where a rapid rate of onset is desired for the final pharmaceutical product. In a preferred embodiment for the drop formulation, the buffering agent most preferably imparts a pH ranging from about 7 to

about 10.5, from about 8 to about 10, from about 8.5 to about 9.5, and most preferably about 9.

Drop formulations are preferably prepared in a three step process comprising (a) dissolving diclofenac in ethyl alcohol to form a solution, (b) mixing said solution with glycerol to form a second solution, and (c) mixing said second solution with water to form a third solution. In a further embodiment, a fourth solution is made by dissolving any desired buffers in water, which is then mixed with the third solution to provide a final solution. The final solution preferably comprises from about 35 to about 45 wt. % water, from about 25 to about 35 wt. % ethyl alcohol, and from about 15 to about 25 wt. % glycerol.

In another embodiment the liquid solution is characterized by its pharmacokinetics, such as C_{max} (i.e. average concentration of active chemical in the bloodstream after oral ingestion), and its t_{max} (i.e. average time to reach said C_{max}). A representative 50 mg. drop diclofenac formulation obtained by the method disclosed in examples 6 and 7 herein exhibits the following pharmacokinetic properties:

C_{max} mean value	1679 ng/ml (CV = 39.85%)
T_{max} mean value	15.0 min (CV = 56%)
AUC_{0-t} mean value	1383 (CV = 30.59%)

Capsule and Tablet Formulations

Examplary solid oral formulations contemplated by the present invention are set forth in Example 12. Preferred C_{max} and t_{max} ranges for tablet and capsule dosage forms of the invention are set forth below:

	Mean C_{max} (ng/ml)	Mean t_{max} (min)
50 mg. diclofenac tablet or capsule	1300-2300; 1400-2200; 1500-2100; 1750-2000; 1600-1900	5-35; 10-30; 12-25; 15-20
25 mg. diclofenac tablet or capsule	700-1150; 750-950; 800-900; 850-1050; 900-1000	5-35; 10-30; 15-30; 15-25
12.5 mg. diclofenac tablet or capsule	350-650; 400-600; 450-550	5-35; 10-30; 15-25

Disintegration times for the tablet and capsule dosage forms of the present invention, when tested according to USP 28 <701>, are preferably less than about 20 minutes, 15 minutes, 10 minutes, 5 minutes, or even 4 minutes, and greater than about 1, 2 or 3 minutes, most preferably from about 3 to about 5 minutes. In one particular embodiment, the dosage form is a tablet, and the tablet has a disintegration time that increases as the hardness of the tablet decreases. In another embodiment, the tablet has a disintegration time that increases as the moisture absorption by the tablet increases.

Dissolution times for the tablet and capsule dosage forms of the present invention, when tested according to USP 28 <711>, based on the time it takes to dissolve 90 or 95 wt. % of the drug substance, are preferably less than about 20 minutes, 15 minutes, 10 minutes, 5 minutes, or even 3 minutes, and greater than about 1 or 2 minutes. In a preferred embodiment the dissolution profile of the dosage forms of the present invention is as follows: not less than 85, 90 or 95% after 15 minutes in simulated intestinal fluid (i.e. water) at pH=6.8.

EXAMPLES

The following examples are put forth so as to provide those of ordinary skill in the art with a complete disclosure and description of how the compounds claimed herein are made and evaluated, and are intended to be purely exemplary of the invention and are not intended to limit the scope of what the inventors regard as their invention. Efforts have been made to ensure accuracy with respect to numbers (e.g., amounts, temperature, etc.) but some errors and deviations should be accounted for. Unless indicated otherwise, parts are parts by weight, temperature is in ° C. or is at room temperature, and pressure is at or near atmospheric.

Example 1

Comparative Study of Diclofenac-K Sachet, Diclofenac-K Tablets, and Placebo in Treatment of Migraine

A randomized, double-blind, double-dummy multi-center, single dose, placebo- and active-controlled crossover study, with an eight hour evaluation was undertaken in adult migraine patients. 328 patients were randomized among treatments and a comparison made among treatments with a 50 mg. diclofenac potassium sachet formulation, the 50 mg. diclofenac potassium sugar coated tablet marketed commercially as Cataflam®, and placebo. Results are reported in Table 1.

TABLE 1

	Pain on Verbal Scale		
Parameter	Diclofenac-K Sachet % of patients	Diclofenac-K Tablet % of patients	Placebo % of patients
Pain free at 2 hours			
ITT pop	24.7%	18.5%	11.7%
PP pop	23.6%	17.8%	12.9%
Mod-sev baseline pain	24.2%	17.0%	12.5%
Headache response 2 hours	46.0%	41.6%	24.1%
Sustained response	36.8%	30.9%	18.4%
Sustained pain free	22.3%	15.1%	9.4%

Example 2

Comparative Study of Diclofenac-K Sachet, Diclofenac-K Tablets, and Placebo in Treatment of Acute Dental Pain

A double-blind, randomized, parallel-group trial compared the analgesic efficacy of single 50 mg doses of diclofenac potassium sachets and tablets with placebo in 184 patients with moderate/severe pain after extraction of impacted third molar(s). The primary efficacy variable was the average pain reduction from baseline during the first 2 hours after intake of study medication, assessed using a visual analog scale (VAS). During the first 2 hours post-dose sachets and tablets demonstrated significantly less pain ($P<0.05$) versus placebo and sachets were more effective than tablets ($P<0.05$). Onset of analgesic effect (VAS) was maintained for

8 hours for sachets and tablets (P<0.05). Fewer patients remedicated versus placebo and the results for pain relief and intensity assessed on a verbal scale confirmed the findings for VAS pain intensity. No safety issues were identified. Results are reported in Table 2.

TABLE 2

Average VAS Pain Reduction from Baseline during the First 2 Hours (ITT Population)

Treatment effect and contrast	N	Average VAS pain reduction in mm: LS mean (SE)	95% CI	P value[a]
Diclofenac Sachet	73	36.3 (2.4)	31.7-41.0	<.0001
Diclofenac Tablet	71	29.1 (2.4)	24.4-33.9	<.0001
Placebo	39	11.7 (3.1)	5.5-17.8	.0002
Diclofenac Sachet - Placebo	—	24.7 (3.8)	17.3-32.1	<.0001 (1)
Diclofenac Sachet - Diclofenac Tablet	—	7.2 (3.1)	1.0-13.4	<.0001 (2)
Diclofenac Tablet - Placebo	—	17.5 (3.8)	10.0-24.9	<.0001 (1)

LS = least squares,

SE - standard error of the mean,

CI—confidence interval.

All statistics for treatment effects and treatment contrasts are based on the analysis of covariance model: Average pain reduction = treatment + country + baseline VAS pain intensity.

[a]P values are two-sided for treatment effects (difference to 0), (1) one-sided P value for verum # placebo, (2) one-sided P value for diclofenac potassium sachet < diclofenac potassium tablet - 10 (non-inferiority test)

Example 3

Representative 900 mg. Powder Sachet Formulation

Table 3 describes the composition of a representative 900 mg. powder sachet formulation containing 50 g. of diclofenac potassium that is suitable for practicing the present invention.

TABLE 3

Name of the component	Unit (mg.)	Function	Reference standard
Diclofenac potassium[1]	50.0	Active substance	Ph. Eur.
Glycerol dibehenate	2.0	Lubricant	Ph. Eur.
Saccharin sodium	5.0	Sweetening agent, Flavoring enhancer	Ph. Eur.
Anise flavor	15.0	Flavoring agent	In-house specifications
Potassium hydrogen Carbonate	22.0	Buffering agent	Ph. Eur.
Mint flavor	35.0	Flavoring agent	In-house specifications
Aspartame	50.0	Sweetening agent, Flavoring enhancer	Ph. Eur.
Mannitol[2]	721.0	Diluent	Ph. Eur. + additional specification
Total weight	900.0		

[1]Particle size distribution:
Not less than 90% ≦500 μm
Not less than 40% and not more than 70% ≦200 μm
Not less than 35% and not more than 65% ≦150 μm
Not less than 30% ≦100 μm
[2]As Mannitol "coarse quality" (648.0 mg) and Mannitol "fine quality" (73.0 mg).

Example 4

Manufacturing Process for 900 mg. Powder Sachets Containing 50 mg. of Diclofenac Potassium

A representative process for manufacturing 900 mg. powder sachets containing 50 mg. of diclofenac potassium is set forth below, using the equipment set forth in Table 1. The manufacture is performed under controlled temperature and relative humidity according to the following process.

Step	
1	Sieve using a vibrating sieving machine (typically 850 μm) 47.45 Kg of Mannitol "fine quality" and 33.15 kg of Diclofenac Potassium. Load in a high shear mixer and mix for approx. 6 minutes. Repeat this step once. (pre-mixture 1)
2	Sieve using a vibrating sieving machine (typically 850 μm), and load in a convection mixer (in the following order) 120.0 kg of mannitol "coarse quality," the pre-mixture 1, 100.0 kg of mannitol "coarse quality," 28.6 kg of potassium hydrogen carbonate, 100.0 kg of mannitol "coarse quality," 65.0 kg of aspartame, 100.0 kg of mannitol "coarse quality," 6.5 kg of saccharin sodium and 100.0 kg of mannitol "coarse quality." Mix for approx. 5 minutes (pre-mixture 2).
3 (final mixture)	Sieve using an oscillating sieving machine (typically 850 μm), and load in the convection mixer, in the following order, 72.4 kg of mannitol "coarse quality," 52.6 kg of the glidant pre-mixture consisting of 2.6 kg of Glyceryl dibehenate and 50.0 kg of mannitol "coarse quality," 45.5 kg of mint flavour, 100.0 kg of mannitol "coarse quality," 19.5 kg of anise flavour and 100.0 kg of mannitol "coarse quality." Mix for approx. 7 minutes in order to obtain the final homogenous mixture to fill into sachets.
4 (filling)	Fill the final mixture into sachets at the target weight.

TABLE 4

Manufacturing equipment

Unit operation	Type of equipment
Sieving	Screening mill, oscillating bar
Premixing (pre-mixture 1)	High shear mixer

TABLE 4-continued

Manufacturing equipment	
Unit operation	Type of equipment
Mixing (pre-mixture 2 and final mixture)	Convection mixer, planetary blenders
Filling into sachet	Powder filler, Volumetric filling station

Example 5

Wet Granulated Powder Sachet Manufacturing Process

The manufacture of 50 mg. diclofenac potassium sachets having the formulation prescribed in Example 3, via wet granulation, is set forth in Tables 5 and 6.

TABLE 5

Batch formula	
Name of the components	Amount (kg)
Diclofenac potassium	11.25[1]
Glycerol dibehenate	0.450
Saccharin sodium	1.125
Anise flavour	3.375
Potassium hydrogen carbonate	4.95
Mint flavour	7.875
Aspartame	11.25
Mannitol "fine quality"	16.425
Mannitol "coarse quality"	145.845
Ethyl Alcohol	3.88*
Total	202.5

*Eliminated during the drying process of the wet granulate.

TABLE 6

Manufacturing process	
Step	
1	Load in a wet granulator 16.2 kg of mannitol "coarse quality," 11.25 kg of diclofenac potassium, 4.95 kg of potassium bicarbonate, 1.125 kg of saccharin sodium and 11.125 kg of aspartame; mix for approx. 5 minutes; add 3.88 kg of ethyl alcohol and mix for 5 minutes; load the wet granulate in oven at 50° C. until the humidity of granulate is below 1%.
2	Sieve using an oscillating sieving machine (typically 850 μm) the following excipients: mannitol "coarse quality," mannitol "fine quality," glyceryl dibehenate, mint flavour and anice flavour; load the granulate obtained in step 1 in a convection mixer and add, in the following order, 129.475 kg of mannitol "coarse quality," 16.425 kg of mannitol "fine quality," 0.45 kg of glyceryl dibehenate, 7.875 kg of mint flavour and 3.375 kg of anise flavour; mix for approx. 30 minutes
3	Fill the final mixture into sachets at the target weight.

Example 6

Representative Drop Formulation (50 mg. Diclofenac Potassium/ml. of Solution)

Table 7 describes a representative formulation for a drop formulation of diclofenac in which one milliliter solution contains 50 mg. of diclofenac potassium. The formulation is administered by adding the drops to water and orally ingesting the mixture.

TABLE 7

Drop Solution Composition			
Names of ingredients	Unit (g)	Function	Reference standards
Active ingredients			
Diclofenac potassium	5.0[a]	Anti-inflammatory agent	Eur. Ph.
Solution excipients			
Ethyl alcohol	30.0	Solubilizing and preservative agent	Eur. Ph.
Glycerol	20.0	Solubilizing agent	Eur. Ph.
Potassium hydrogen carbonate	2.5	Buffering agent	Eur. Ph.
Saccharin sodium	1.5	Sweetening agent	Eur. Ph.
Caramel E 150a	0.25	Colouring agent	Int. standard[b]
Purified water	42.9	Diluent agent	Eur. Ph.
Total weight[b]	102.15		

[a]This amount refers to active substance material with 100.0% assay.
[b]Weight of 100.0 ml of solution (relative density = 1.0215 g/ml).

The formulation is preferably contained in a brown colored glass container, equipped with dropper and screw-cap closure, holding 20 or 100 ml of Diclofenac potassium solution. The glass container (type III) is suitable for liquid preparations that are for parenteral use. The dropper is made from polyethylene low density (PE-LD) material, according to food and pharmaceutical regulations. The screw cap is made from polypropylene, suitable as child proof closure.

Example 7

Manufacturing Process for Drop Formulation

The raw materials necessary for the production of a pilot standard batch of 250 liters of solution (volume required to fill 12,500 or 2,500 bottles with a capacity of 20 ml or 100 ml, respectively) are listed in Table 8.

TABLE 8

Manufacturing formula for a pilot standard batch of 250 liters of solution	
Names of Ingredients	Unit (kg)
Active ingredients	
Diclofenac potassium[a]	12.500
Solution excipients	
Ethyl alcohol 96%	75.000
Glycerol	50.000
Potassium hydrogen carbonate	6.250
Saccharin sodium	3.750
Caramel E 150a	0.625
Purified water	107.250
Total weight[b]	255.375

[a]Analytical specifications of Diclofenac potassium are the same used for the sachets
[b]Weight of 250 liters of solution (relative density 1.0215 g/ml).

12.5 kg of Diclofenac potassium, 6.25 kg of potassium hydrogen carbonate, 75 kg of ethyl alcohol 96%, 50 kg of glycerol, 3.75 kg of saccharin sodium, 0.625 kg of Caramel E

150a and two different amounts (76 kg and 31.25 kg) of purified water are first weighed.

A first mixture is then prepared by adding the ethyl alcohol 96% into a mixing vessel and then, under stirring, adding the active ingredient diclofenac potassium. After stirring for 10-15 minutes, the glycerol is added and the mixture stirred for another 10-15 minutes. While stirring, 76 kg of purified water is added to the mixture and stirred until a complete clear solution is obtained.

A second mixture is prepared by adding 31.25 kg of purified water into a separate mixing vessel and, under stirring, adding the remaining excipients (potassium hydrogen carbonate, saccharin sodium and Caramel E 150a). The mixture is stirred for 15-30 minutes.

While stirring, the first mixture is added to the second mixture and the resultant mixture stirred until a complete clear brown solution is obtained. Under mixing, water is added to the solution until a weight of 255.375 kg (250 liter of solution) is obtained. The solution is particle-free filtrated.

Example 8

Additional Drop Formulations (25 mg. Diclofenac Potassium/ml)

Tables 9 and 10 describe representative formulations of drops containing 25 mg. of diclofenac potassium per ml. of solution.

TABLE 9

Names of ingredients	Unit (g)	Function	Reference standard
Active ingredients			
Diclofenac potassium	2.50	Anti-inflammatory agent	Eur. Ph.
Solution excipients			
Ethyl alcohol 96%	30.00	Solubilizing and preservative agent	Eur. Ph.
Glycerol	20.00	Solubilizing agent	Eur. Ph.
Potassium hydrogen carbonate	1.25	Buffering agent	Eur. Ph.
Saccharin sodium	1.50	Sweetening agent	Eur. Ph.
Acesulfame	3.00	Sweetening agent	Eur. Ph.
Caramel E 150a	0.25	Colouring agent	Int. standard
Mint flavour	1.40	Flavouring agent	Int. standard
Anise flavour	0.60	Flavouring agent	Int. standard
Purified water	Qb to 100 ml	Diluent agent	Eur. Ph.
Total volume	100.00		

TABLE 10

Names of ingredients	Unit (g)	Function	Reference standard
Active ingredients			
Diclofenac potassium	2.50	Anti-inflammatory agent	Eur. Ph.
Solution excipients			
Ethyl alcohol 96%	30.00	Solubilizing and preservative agent	Eur. Ph.
Glycerol	20.00	Solubilizing agent	Eur. Ph.
Potassium hydrogen carbonate	1.25	Buffering agent	Eur. Ph.
Saccharin sodium	1.50	Sweetening agent	Eur. Ph.
Acesulfame	3.00	Sweetening agent	Eur. Ph.
Caramel E 150a	0.25	Colouring agent	Int. standard
Cola flavour	2.00	Flavouring agent	Int. standard
Purified water	qb a 100 ml	Diluent agent	Eur. Ph.
Total volume	100.00		

Example 9

900 mg. Powder Sachet Formulation Containing 25 mg of Diclofenac Sodium

The ingredients of the product diclofenac sodium 25 mg powder for oral solution (sachets, weighing 900.0 mg) are listed in Table 11 below.

TABLE 11

Names of ingredients	Unit (mg.)	Function	Reference standard
Active ingredients			
Diclofenac sodium	25[a] mg	Anti-inflammatory agent	Eur. Ph.
Excipients			
Potassium hydrogen carbonate	11.0 mg	Buffering agent	Eur. Ph.
Mannitol[b]	698.0 mg	Diluent agent	Eur. Ph.
Mannitol[c]	74.00 g	Diluent agent	Eur. Ph.
Acesulfame Potassium	40.0 mg	Sweetening agent	Eur. Ph.
Glycerol Dibehenate (compritol 888 ATO)	2.0 mg	Lubricant agent	Eur. Ph.
Mint flavour	15.0 mg	Flavouring agent	Manufacturer
Anise flavour	35.0 mg	Flavouring agent	Manufacturer
Total weight	900.0 mg		

[a]This amount refers to active substance material with 100.0% assay. The diclofenac sodium has the following particle size distribution: not less than 95% of the particles are less than 500 micrometers in diameter, not more than 90% are less than 250 micrometers in diameter, not more than 60% are less than 180 micrometers in diameter, and not more than 30% are less than 125 micrometers.

[b]Pearlitol SD 200, conform to Eur. Ph.

[c]Mannitol 35, conform to Eur. Ph..

Example 10

Method of Preparing 900 mg. Powder Sachets Containing 25 mg. of Diclofenac Sodium

A representative process for manufacturing 900 mg. powder sachets containing 25 mg. of diclofenac sodium is set forth below, using the equipment set forth in Table 1. The manufacture is performed under controlled temperature and relative humidity according to the following process.

Preparation of the Pre-mixture

Sieve all the ingredients necessary for the production of the powder, then weigh 1.375 kg of diclofenac sodium, 0.605 kg of potassium hydrogen carbonate, 38.390 kg of mannitol (pearlitol SD 200), 4.070 kg of mannitol 35, 2.200 kg of acesulfame K, 0.825 kg of mint flavour, 1.930 kg of anise flavour and 0.11 kg of glyceryl dibehenate. Load in the mixer: diclofenac sodium, potassium hydrogen carbonate, mannitol 35, acesulfame K, mint flavour and anise flavour. Mix for 25 minutes.

Preparation of the Mixture

Transfer the premix into mixer; add mannitol SD 200 and glyceryl dibehenate, mix for 30 minutes.

Example 11

Diclofenac K Sachet Bioavailability Comparison

Test Formulations: Diclofenac potassium 50 mg powder for oral solution (Example 4)

Reference Formulation: Diclofenac potassium, 50 mg film-coated tablets, Cataflam by Novartis Pharma

TABLE 12

	Test Formulation fasting					
Statistic	AUC(0-inf) (ng * hr/mL)	AUC(0-t) (ng * hr/mL)	Cmax (ng/mL)	Tmax (hr)	Kel (l/hr)	T½ (hr)
N	32	33	33	33	32	32
Geometric mean	1201.001	1185.573	1505.296	0.264	0.54616	1.269
Mean	1232.925	1216.609	1586.502	0.277	0.56938	1.322
SD	283.9458	277.7587	513.3048	0.1035	0.167653	0.3803
CV %	23.03	22.83	32.35	37.32	29.45	28.76
Median	1177.67	1164.38	1528.20	0.25	0.5389	1.29
Minimum	686.48	668.10	800.58	0.17	0.3442	0.74
Maximum	1912.34	1896.02	2800.55	0.67	0.9352	2.01

TABLE 13

	Cataflam fasting					
Statistic	AUC(0-inf) (ng * hr/mL)	AUC(0-t) (ng * hr/mL)	Cmax (ng/mL)	Tmax (hr)	Kel (l/hr)	T½ (hr)
N	32	33	33	33	32	32
Geometric mean	1064.370	1045.187	1037.124	0.618	0.56098	1.236
Mean	1097.185	1077.596	1146.649	0.788	0.58669	1.290
SD	275.9971	272.7532	450.9879	0.7524	0.182630	0.3808
CV %	25.16	25.31	39.33	95.53	31.13	29.51
Median	1078.28	1059.80	1125.91	0.50	0.5843	1.19
Minimum	537.38	524.43	197.17	0.25	0.3378	0.63
Maximum	1975.32	1959.12	1972.74	4.00	1.1013	2.05

Example 12

50 mg. Diclofenac K Tablet Comparison

Test Formulations: T1: Diclofenac potassium 50 mg film-coated tablets, alcohol granulation T2: Diclofenac potassium 50 mg film-coated tablets, dry granulation
Reference Formulation: Diclofenac potassium, 50 mg film-coated tablets, Voltarene® Rapid by Novartis Pharma
Study design: Single dose, 3-way, crossover randomised on 6 healthy volunteers
Blood samples drawn: 0 (pre-dose), 5, 10, 15, 20, 30, 45, 60, 90 min, 2, 3, 4, 5, 6, 8, 10, 12 h
Assay: LC-MS-MS//LOQ 5 ng/ml

TABLE 14

Formulation of Comparison Tablets

	T1, K salt, 50 mg, tablets	T2, K salt, 50 mg, tablets	Reference, K salt, 50 mg, Voltaren ® Rapid tablets
Description	Diclofenac potassium 50 mg film-coated tablets (by alcoholic granulation)	Diclofenac potassium 50 mg film-coated tablets (by direct compression)	Diclofenac potassium 50 mg film-coated tablets
Active ingredient	Diclofenac potassium mg 50	Diclofenac potassium mg 50	Diclofenac potassium mg 50
Excipients	Potassium bicarbonate mg 22 Mannitol mg 50 Maize starch mg 25 Hydroxypropylmethylcellulose mg 0.2 Sodium laurylsulfate mg 0.1 Polyvinylpyrrolidone mg 1 Sodium starch glycollate mg 2.5 Magnesium stearate mg 4.5 Silicium aerosil FK 160 mg 1 Coating Opadry Clear (HPMC 2910 and polyethyleneglycol 400) mg 4	Potassium bicarbonate mg 22 Mannitol 400 mg 119.9 Sodium laurylsulfate mg 0.1 Polyvinylpyrrolidone mg 6 Magnesium stearate mg 2 Film Coating Opadry Clear (HPMC 2910, polyethyleneglycol 400) mg 4	Calcium phosphate Saccharose Maize starch Talc Sodium carboxymethylcellulose Colloidal anhydrous silicium Polyvinylpyrrolidone Microcrystalline cellulose Magnesium stearate Polyethylenglycole Titanidioxide (E171) Iron oxide red (E172)
Total weight	160.3 mg	204 mg	

TABLE 15

Pharmacokinetics of Comparison Tablets

		PK results		
		Test 1 (K, tablets 50 mg)	Test 2 (K, tablets 50 mg)	Reference (K, tablets 50 mg)
C_{max}	Mean	1873.30	1744.8	1307.0
	SD	553.80	572.3	558.4
	CV %	29.5	32.8	42.7
	Min	1228.9	1057.4	581.8
	Max	2516.5	2468.9	1935.5
AUC	Mean	1219	1237	1168
	SD	246	276	282
	CV %	20.2	22.3	24.1
	Min	874	848	913
	Max	1615	1668	1642
t_{max}	Mean	0.31 h (18.6 min)	0.28 h (16.8 min)	0.68 h (40.8 min)
	SD	0.04	0.07	0.65
	CV %	12.9	25.0	95.6
	Min	0.25 h (15 min)	0.17 h (10.2 min)	0.25 h (15 min)
	Max	0.33 h (19.8 min)	0.33 h (19.8 min)	2.00 h (120 min)

Throughout this application, various publications are referenced. The disclosures of these publications in their entireties are hereby incorporated by reference into this application in order to more fully describe the state of the art to which this invention pertains. It will be apparent to those skilled in the art that various modifications and variations can be made in the present invention without departing from the scope or spirit of the invention. Other embodiments of the invention will be apparent to those skilled in the art from consideration of the specification and practice of the invention disclosed herein. It is intended that the specification and examples be considered as exemplary only, with a true scope and spirit of the invention being indicated by the following claims.

What is claimed is:

1. A method of treating migraine associated with phonophobia and photophobia in a human patient within two hours of administration comprising:

a) providing a liquid formulation comprising about 50 mg. of diclofenac or a pharmaceutically acceptable salt thereof in combination with an alkali metal carbonate or bicarbonate, wherein said formulation:

i) is provided as a powder formulation and dissolved or suspended in water immediately before administration, or as a liquid formulation that is ingested with or without further mixing;

ii) optionally has been found to achieve a maximum plasma concentration (C_{max}) (arithmetic mean) of from about 1500 to about 2500 ng/ml; and

iii) has been found to achieve a time to maximum plasma concentration (t_{max}) (arithmetic mean) in from about 10 to about 25 minutes;

b) orally administering said formulation to a patient suffering from migraine associated with photophobia and phonophobia, and

c) thereby relieving said photophobia and said phonophobia in said patient within two hours of administration.

2. The method of claim 1 wherein said patient is suffering from migraine that requires sustained migraine relief for at least 24 hours.

3. The method of claim 1 wherein said liquid formulation comprises about 50 mg. of diclofenac potassium.

4. The method of claim 1 wherein said formulation has been found to achieve t_{max} in from about 10 to about 20 minutes.

5. The method of claim 1 wherein said formulation is provided as a powder formulation, further comprising dissolving or suspending said powder in water immediately before administration.

6. A method of treating recurrent migraine requiring 24 hour treatment in a human patient suffering from migraine comprising:

a) providing a liquid formulation comprising about 50 mg. of diclofenac or a pharmaceutically acceptable salt thereof in combination with an alkali metal carbonate or bicarbonate, wherein said formulation:

i) is provided as a powder formulation and dissolved or suspended in water immediately before administration, or as a liquid formulation that is ingested with or without further mixing;

ii) optionally has been found to achieve a maximum plasma concentration (C_{max}) (arithmetic mean)of from about 1500 to about 2500 ng/ml; and

iii) has been found to achieve time to maximum plasma concentration (t_{max}) (arithmetic mean) in from about 10 to about 25 minutes;

b) orally administering said formulation to said patient; and

c) thereby providing sustained migraine relief to said patient for at least 24 hours.

7. The method of claim 6 wherein said patient suffers from headache pain and either photophobia or phonophobia or both.

8. The method of claim 6 wherein said liquid formulation comprises about 50 mg. of diclofenac potassium.

9. The method of claim 6 wherein said C_{max} has been found to have an inter-subject variability of less than about 70%.

10. The method of claim 6 wherein said t_{max} has been found to have an inter-subject variability of less than about 70%.

11. The method of claim 6 wherein said formulation has been found to achieve t_{max} in from about 10 to about 20 minutes.

12. The method of claim 6 wherein said formulation is provided as a powder formulation, further comprising dissolving or suspending said powder in water immediately before administration.

13. A method of treating migraine in a human patient, including headache pain, nausea, photophobia and phonophobia, within two hours after administration, comprising:

a) providing a liquid formulation comprising about 50 mg. of diclofenac or a pharmaceutically acceptable salt thereof in combination with an alkali metal carbonate or bicarbonate, wherein said formulation:

i) is provided as a powder formulation and dissolved or suspended in water immediately before administration, or as a liquid formulation that is ingested with or without further mixing;

ii) optionally has been found to achieve a maximum plasma concentration (C_{max}) (arithmetic mean) of from about 1500 to about 2500 ng/ml; and

iii) has been found to achieve time to maximum plasma concentration (t_{max}) (arithmetic mean) in from about 10 to about 20 minutes;

b) orally administering said formulation to a patient suffering from migraine, including headache pain, nausea, photophobia and phonophobia; and

c) thereby treating said migraine, headache pain, nausea, photophobia and phonophobia in said patient within two hours of administration, wherein said migraine is defined as a disease manifested in a population of patients by periodic attacks of headache pain, nausea, photophobia and phonophobia.

14. The method of claim 13 wherein said patient suffers from headache pain and either photophobia or phonophobia or both.

15. The method of claim 13 wherein said C_{max} has been found to have an inter-subject variability of less than about 70%.

16. The method of claim 13 wherein said t_{max} has been found to have an inter-subject variability of less than about 70%.

17. The method of claim 13 wherein said liquid formulation comprises about 50 mg. of diclofenac potassium.

18. The method of claim 13 wherein said formulation has been found to achieve t_{max} in from about 10 to about 20 minutes.

19. The method of claim 16 wherein said formulation is provided as a powder formulation, further comprising dissolving or suspending said powder in water immediately before administration.

20. A method of treating headache pain, nausea, phonophobia and photophobia in a human patient within two hours of administration comprising:

a) providing a pharmaceutical formulation comprising about 50 mg. of diclofenac or a pharmaceutically acceptable salt thereof in combination with an alkali metal carbonate or bicarbonate, wherein said formulation:

i) has been found to achieve an average maximum plasma concentration (C_{max}) (arithmetic mean) of from about 1400 to about 2500 ng/ml; and

ii) has been found to achieve an average time to maximum plasma concentration t_{max} (arithmetic mean) in from about 10 to about 35 minutes; and

b) orally administering said formulation to a patient suffering from photophobia and Phonophobia;

thereby treating said headache pain, nausea, photophobia and phonophobia within two hours of administration.

21. The method of claim 20 wherein said formulation has been found to reach a C_{max} of greater than 1500 ng/ml, and a t_{max} of less than 30 minutes, and further wherein said C_{max} has been found to reach an average C_{max} when tested in a fasted state, and said t_{max} has been found to reach an average t_{max} when tested in a fasted state.

22. A method of treating recurrent migraine requiring 24 hour treatment in a human patient suffering from migraine, and providing relief from said migraine for at least 24 hours without rebound, comprising:

a) providing a pharmaceutical formulation comprising about 50 mg. of diclofenac or a pharmaceutically acceptable salt thereof in combination with an alkali metal carbonate or bicarbonate, wherein said formulation:

i) has been found to achieve an average maximum plasma concentration (C_{max}) (arithmetic mean) of from about 1400 to about 2500 ng/ml; and

ii) has been found to achieve an average time to maximum plasma concentration t_{max} (arithmetic mean) in from about 10 to about 35 minutes; and

b) orally administering said formulation to said patient;

thereby treating said recurrent migraine and providing relief from said migraine for at least 24 hours without rebound.

23. The method of claim **22** wherein said formulation has been found to reach a C_{max} of greater than 1500 ng/ml, and a t_{max} of less than 30 minutes, and further wherein said C_{max} has been found to reach an average C_{max} when tested in a fasted state, and said t_{max} has been found to reach an average t_{max} when tested in a fasted state.

24. A method of treating headache pain, nausea, phonophobia and photophobia in a human patient within two hours of administration comprising:

a) providing a pharmaceutical formulation comprising about 50 mg. of diclofenac or a pharmaceutically acceptable salt thereof in combination with an alkali metal carbonate or bicarbonate, wherein greater than 90% of said diclofenac dissolves completely in 50 ml. of water at 25° C. under continuous stirring for fifteen minutes at pH 6.8; and

b) orally administering said formulation to a patient suffering from photophobia and phonophobia, and thereby relieving said photophobia and phonophobia within two hours of administration.

25. A method of treating recurrent migraine requiring 24 hour treatment in a human patient suffering from migraine comprising:

a) providing a pharmaceutical formulation comprising about 50 mg. of diclofenac or a pharmaceutically acceptable salt thereof in combination with an alkali metal carbonate or bicarbonate, wherein greater than 90% of said diclofenac dissolves completely in 50 ml. of water at 25° C. under continuous stirring for fifteen minutes at pH 6.8;

b) orally administering said formulation to said patient;

thereby treating said recurrent migraine for at least twenty four hours after administration.

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